



ATLAS CHEMICAL INDUSTRIES, INC.

WILMINGTON, DELAWARE 19899

September 26, 1967

Dr. William A. Knapp
Allied Chemical Corporation
P. O. Box 405
Morristown, N. J. 07960

Dear Dr. Knapp:

Re: Proposed FDA Food Additive
Procedural Regulations

Pursuant to the decision at the recent Food, Drug and Cosmetic Chemicals Committee meeting of MCA, I submit the following rough comments on these regulations. I hope they will reach you in time to do some good and regret that I could not get them out earlier. In view of the time element, I include most of my thoughts without paying particular attention as to whether or not it is desirable in any particular instance to protest. I might comment, however, that in recent years, particularly in the drug field, objections on the ground that a procedural regulation was vague and indefinite only resulted in FDA's revision to include a lot of specific requirements that were probably equally objectionable, although perhaps for different reasons. My comments follow:

In Section 121.9(a) in the first two lines I suggest that "submitting or intending to submit a food additive petition" be deleted. In most instances the person submitting the master file is not submitting or intending to submit a food additive petition. He is submitting the master file on his confidential information so that FDA may use it in connection with a food additive petition filed by someone else.

The last sentence of this same paragraph appears to limit the use of these master files to use in food additive petitions. Many of our materials are used as adjuncts in connection with foods, drugs, colors and pesticides. In view of the voluminous nature of many of these master files, it is believed that one master file should suffice for all of these fields.

Section 121.9(c) was discussed briefly at the committee meeting. As I indicated at that time, I feel that we are lucky

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that only a summary of the toxicology is not considered confidential, and therefore would not object.

Section 121.50(a) in lines 9 and 10 state that published information in support of a petition shall be submitted "in reprint form." If the term "reprint" is used in its normal connotation, namely reprints produced by the publisher, this is not satisfactory because the publisher or the author may refuse to allow production of such reprints. It seems to me that this should be clarified to clearly permit submission of articles produced with any normal reproduction process.

In this same paragraph the next to last sentence requires that unpublished scientific studies include identification of the scientists who did the work and their pertinent qualifications. It seems to me that this places an unnecessary burden on the petitioner, particularly with respect to scientific studies having to do with such matters as food technology, reproducibility of the food additive, the development of analytical methods, etc. The sentence as worded might even have to do with the basic development of the process of manufacture. I should like to see this limited to safety or toxicology studies if it is retained. Even with toxicology studies this might present a problem in the case of work conducted eight to ten years ago.

Section 121.50(b) provides that information previously submitted "by the petitioner" to FDA may be incorporated in subsequent submissions provided that the submission is in "a food additive master file kept current by the petitioner" or "is in another form of submission not over ten years old." As previously indicated, it is not usually the petitioner who is maintaining the master file. Consequently, it is believed that reference to the petitioner should be deleted. Secondly, the elimination of submissions over ten years old should not be included. In the first place, these older submissions were in many instances not designated "food additive master file." They were merely given a master file number. In the second place, no reason is seen why ten year old submissions should be eliminated.

Section 121.50(c) should be amended to state that the double spacing, page size requirements and margin requirements shall not be applicable to old unpublished scientific data, or to publications as this would require a terrific amount of work in reproduction to size, etc. Neither should it be applicable to ordinary laboratory reports which are generally not double spaced, for example.

In Section 121.50(e)(I)(B)(2) and (5) my objection here is to the inclusion of "maximum" quantity of the food additive to be expected in the total daily diet and to the inclusion in subparagraph 5 of "any comparable substances." See line 6 from the bottom. While average consumption of various foods in the U. S. can be determined from Department of Agriculture tables, it is my understanding that maximum consumption by any particular consumer is not available from any source and in any event is not required because the safety factor employed (usually 100) in judging the safety of the particular food use on the basis of animal toxicity studies is supposed to take care of the variations in consumption by individual consumers. Unfortunately at this point I do not have this documented and it may be that it cannot be documented because no one seems to be very clear as to the derivation of the safety factor of 100.

In addition, "any comparable substances" is indefinite because it does not state the basis of comparability. Thus, many substances are comparable from a view point of their effect in foods but are not comparable at all from a safety or toxicity or chemical viewpoint. This type of language has caused a great deal of trouble in reporting on new drugs where one is supposed to also report adverse reactions on comparable drugs.

These objections with regard to maximum levels also apply to sections falling under "II. Body of the Petition." as, for example, "B. Use." first unnumbered paragraph and subparagraph 2.

Under "II. Body of the Petition." A. Identity, 1. Direct Additive, (b) Description of the additive, subparagraphs iv, v, vi, and vii regarding manufacturing processes, specifications, reproducibility and stability data are objectionable in that they do not exclude this type of data where this data is unnecessary for one reason or another. For example, present regulation 121.51(c) A. in the second paragraph says some of these types of information shall be supplied "When the chemical identity and composition is not known,". I suggest this qualification be applied to all these subparagraphs. Examples would be petitions for new uses for additives already included in the Food Additive Regulations, Food Chemicals Codex, U.S.P., N.F., etc.

The first paragraph of Section II, A, 2, a, of the food additive petition set forth in 121.50(e) relates to indirect additives and recognizes two types, namely those added for functional use in production and those in food contact surfaces. This comment relates to the latter.

As a practical matter and for purposes of clarity, the petition framework should recognize that there are at least two aspects of food contact surfaces which are not necessarily amenable to uniform treatment. The first of these is the basic substrate of the contact surface such as cellophane, polyethylene, etc. The second constitutes the large group of adjuvants or ingredients used in or on the basic substrate.

In existing food additives Subpart F relating to food additives resulting from contact with containers or equipment, these two types of additives from food contact surfaces are treated in at least three different manners.

Some of the regulations define only the basic substrate leaving the definition of suitable adjuncts to other regulations in Subpart F. Examples of such regulations are 121.2510 Polyethylene and 121.2521 Vinyl Chloride-Propylene Copolymer.

A second type of regulation defines the composition of the basic substrate and also in the same regulation lists optional adjuvants that may be incorporated in or added to the basic substrate. An example of this type of regulation is 121.2522 Polyurethane Resins. Or such a regulation may list the adjuvants and also provide for the use of other adjuvants included in any other regulation as safe for use as a component. Such a regulation is 121.2507 Cellophane. See 121.2507(b)(3).

A third type of regulation lists classes of adjuvants that may be in or on any of the approved food contact surfaces. Such a regulation is 121.2541 Emulsifiers and/or Surface Active Agents.

Section II, A, 2, b, and particularly portions of subparagraphs iii, iv and v are confusing and inapt in that they tend to treat the adjuvants for food contact surfaces in terms of the food contact surfaces. For example, subparagraph iii requires "Manufacturing process, including for food contact surfaces the raw materials and their specifications that encompass the basic resin polymer and the adjuvants (such as plasticizers, stabilizers, preservatives, fillers, colorants, catalysts, etc.) along with the analytical technique used to check the specifications***."

If it be assumed that the basic substrate is an approved food contact surface, as it will be in many instances where a new adjuvant is proposed, it is not believed that this information should be required for the basic food contact surface or substrate.

If it can be said that subparagraph iii is not applicable to a new adjuvant, we then turn to subparagraph iv which reads in part "Specifications for the additive(s) in food contact surfaces, including their identities, the minimum content of the desired component(s), and the limitations or impurities including total heavy metals, monomers, catalyst residues, etc. **** Data from a suitable number of representative production batches of the food contact surfaces shall be included to establish the range of impurities and by-products to be expected and to show that the proposed specifications can be met." (Emphasis ours.)

It is submitted that data from representative production batches of the food contact surfaces are not appropriate to show that the specification for the adjunct additive can be met. If the requirement that data from a suitable number of representative production batches is kept (see above comment regarding subparagraphs iv, v, vi and vii under A, Identity, 1. Direct Additive (b) Description of the Additive) it would seem that this should be "representative production batches of the additive(s).

Again in subparagraph v. we find the requirement

"Reproducibility of the food contact surfaces including the production controls and tests employed to assure that a reproducible product will be manufactured."

If this requirement is to be retained (see above comment regarding subparagraphs iv, v, vi, and vii under A. Identity, 1, Direct Additive (b) Description of the Additive), it should not be applicable to adjuvants particularly for adjuvants for substrate food contact surfaces that have already been approved in the regulations.

Continuing in the Food Additive Petition, D. Methods, subparagraph 4, it seems to me that the specifications for food contact surfaces referred to here are no different than those referred to in A, 2, b, iii, and iv, which require the analytical methods for each specification. This would appear to be duplication of information on the "tests" or "analytical methods."

Section E. It seems to me that we should strive for some sort of grandfather clause for new uses for food additives, particularly direct additives, that are already in the regulations. Otherwise we may be required to reorganize and resubmit all the safety data in the form provided in this section for a new use.

Further with respect to the requirement that an estimate of the maximum consumption of the additive be submitted, I understand the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" written by FDA staff members and published by the Association of Food and Drug Officials of the United States in 1959 relates the sensitivity of man to various species of animals. The highest ratio is that man is 10 times as sensitive as the cat and rat. The arbitrary safety factor of 100 therefore provides another ten-fold difference to take care of other variables including consumption.

Also the Second Report of the Joint FAO/WHO Expert Committee on Food Additives "Procedures for the Testing of International Food Additives to Establish Their Safety for Use", WHO Technical Report Series #144, 1958, says on page 17:

"From these various investigations a dosage level can be established that causes no demonstrable effect in the animals used. In the extrapolation of this figure to man, some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease processes in the human population, the difficulty of estimating the human intake and the possibility of synergistic action among food additives.

It will be useful to try to define here the standard daily dietary dose. This is taken to be the amount of the food additive that might be expected to be consumed by an average adult eating a normal diet as determined from some appropriate dietary survey. It should be assumed in these calculations that all the foods likely to be treated with the additive will contain it at the level proposed.

It is inescapable that some arbitrary factor must be applied in order to provide an adequate margin of safety. Where the maximum ineffective dose in animals is calculated in g/kg body-weight, a margin of safety of the order of 100 has been widely used. In the absence of any evidence to the contrary, the Committee believes that this margin of safety is adequate."

It is hoped that the foregoing will be of assistance.

Very truly yours,



Kenneth E. Mulford
Assistant to the President

KEM:HP

CC: Mr. James Hulse
Dr. G. P. Vincent
Mr. M. M. Hoover