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FDCC Subcommittee on FDA Procedural Regulations

TO: Dr. George P. Vincent
Mr. James W. Hulse

The attached compilation of comments of FDA Procedural Regulations includes more points of discussion than were agreed to at our last meeting because on reconsideration I felt that the MCA commentary should include all questions we could not ourselves resolve. Also, I felt it would be easier to delete than to compose language at our next meeting now set for Wednesday, October 11 at Morristown if we find no opportunity to meet earlier.

Will you please contemplate tone of introductory remarks to FDA.

Very truly yours,

W. A. Knapp

WAK:dmk
Encl.
cc: Mr. Morgan Hoover

§121.7 Food additives for use in feed and drinking water of animals and food additives that are also new drugs, certifiable antibiotic drugs and/or pesticides.

§121.7 (a) (3)

We suggest that this subsection should be revised to delete the word "chemical" prior to the word "assay." It is strongly urged that to limit the assay methods acceptable to chemical methods is an unneeded and illogical restriction as there may be practical biological, physical or other methods which cannot be technically defined as "a chemical" assay. The imposition of such a restriction would unduly limit the constant search by quality control personnel for better and more practical methods of assay, some of which may be other than chemical methods. Neither §505 nor §409 of the Food, Drug and Cosmetic Act (the latter indicating that the methods for determining the quantity of additives in or on foods should be practicable) require that such methods be limited to chemical methods.

§121.9 Food additive master files.

§121.9 (a)

In the first two lines it is suggested either that the words "submitting or intending to submit a food additive petition" be deleted or the words "or support" be added following the words "intending to submit." In many 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 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.

§121.9 (c)

Many chemical manufacturers are deeply concerned that the confidentiality of submissions in support of proposed regulations will not be retained as in the past. Subsection 121.9 (c) excludes from confidential protection the analytical methods and the summary of the toxicological basis on which a food additive regulation is based. Presumably, this section applies to such information as may be submitted to a master file but not to that which forms a part of the petition required in §121.50.

§121.50 (f) states, "The scientific bases of safety on which any food additive regulation rests, including food additive analytical methods and a summary of the toxicological data, are not considered confidential." In our opinion, §121.50 (f) is considerably broader than §121.9 (c) since §121.50 (f) could be construed as excluding from confidential protection all petition information including basic studies and raw data to the extent that such information could be considered relevant to "the scientific bases of safety." In addition, the summary of toxicological data referred to in §121.9 (c) and §121.50 (f) may be the detailed toxicological summary

required as part of a food additive petition described in I (Introduction) B.5. in proposed §121.50. We believe that toxicological information developed at a petitioner's expense and especially the details thereof, such as methodology and raw data, should be given the same confidential protection given to trade secrets. While knowledge of the analytical techniques employed may be necessary for enforcement purposes and therefore subject to public disclosure, the toxicological data or any in depth detailed summary thereof is not needed for enforcement purposes and should therefore be kept confidential unless the petitioner is willing to publish same or authorize its public disclosure. Accordingly, we recommend reference to the toxicological summary be deleted from §121.9 (c) and §121.50 (f) or, at the very least, that §121.50 (f) be revised to be consistent with §121.9 (c) and that both sections be revised to make it clear that the summary referred to is not the detailed summary required in the petition by section I.B.5.

§121.50 Content and form of food additive petitions.

§121.50 (a)

Under this section "any published information used in support of the petition shall be submitted in reprint form." We submit (1) that the term "reprint" in the normal connotation may be denied by author or publisher, (2) that such reprints are normally available only for a limited time following the journal publication and (3) that they are infrequently, if ever, of the 8 x 10-1/2" size required by the proposed subsection (c) of this regulation. For these reasons we suggest that the words "or readable copy" be inserted following "reprint form."

Also, with respect to the same subject it is noted that §130.37 of New Drug Regulations waives submission of reprints from a large number of journals available in the Food and Drug Administration library. It is suggested that petitions for food additive regulations similarly be permitted to include material in the FDA library by reference, if the petitioner so desires.

Subsection (a) also states that "All original unpublished scientific studies supplied in the petition shall include identification of the scientists who did the work and their pertinent qualifications." In many instances, it will be impossible to determine the identity and qualifications of all of the various chemists, toxicologists and other scientists who participated in the study involved. However, assuming that such a requirement would be necessary, we would recommend that it follow the regulatory precedent of Regulation §130.4 (c), the form for new drug applications, subsection 2.8 (b) of which requires a "description of the qualifications including educational background and experience of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength . . .," etc. Following this precedent, this sentence could be revised to read, "With all original unpublished scientific studies supplied, the petition shall provide a description of the qualifications, including educational background and experience, of the technical and professional personnel who were responsible for assuring the accuracy and reliability of such studies, together with a statement of their responsibilities."

§121.50 (b)

Section 121.50 (b) provides for the incorporation by reference of previous submissions where the previous submission " . . . is in a food additive master file kept current by the petitioner, or is in another form of submission not over 10 years old."

We do not understand the intent or meaning of this 10 year limitation. By implication, one could conclude that any data over 10 years old is deemed to be unreliable unless in a master file kept current. We suggest that many submissions whether part of master files (formerly designated "master files" or now designated "food additive master files"), petitions, new drug applications, or data leading to prior sanctions or approvals are of permanent value regardless of age. For example, detailed toxicological studies submitted in 1950 which led to a prior sanction or approval are still valid in many cases and data in food additive petitions filed since the effective date of the Food Additives Amendment may still be valid although over 10 years old.

The net effect of such a 10-year limit on submissions other than master file submissions is to force petitioners to establish master files for intentional or incidental food additive products. We see no justification for imposing this added burden on a petitioner whose formal petition filing should constitute an adequate file record. The only burden petitioner should have in connection with the reference to data already on file with FDA is a requirement of an accurate description in sufficient detail to provide adequate identification thereof and a statement reaffirming the current validity of any conclusions therein.

For the above reasons, we would suggest deletion of the 10-year limitation for submissions other than those in a "master file kept current."

§121.50 (c)

This section prescribes paper size, line spacing, typing margins, hole punchings, etc., which must be used in connection with petitions. There are many reasons which would make compliance difficult. Some are the following:

(1) Except for legal purposes, the vast majority of U.S. business establishments use only 8-1/2" x 11" paper for correspondence, report writing, etc. It is difficult to obtain any other size from most stationers except on special order at extra cost. Carbon paper of different size presents similar difficulties.

(2) Photo-reproduction papers are likewise of 8-1/2" x 11" dimension requiring hand trimming to bring to size prescribed.

(3) It is often desirable for the sake of completeness to include past studies rather than incorporate same by reference. The proposed regulation would require re-typing of thousands of pages of text and photoreduction of graphs or pictures to bring to proper size.

(4) As noted in comments on §121.50 (a) above, reprints or photo-reproductions of journal articles are usually not of the prescribed size and would require photoreduction or enlargement at needless and great expense.

(5) Similarly, reports of outside investigators (toxicologists, consultants, analysts, etc.,) are all on paper of 8-1/2" x 11" dimension and would require re-typing or other reproduction to the size prescribed.

(6) File cabinets, file folders, record boxes, ring binders, etc., are made to accommodate 8-1/2" x 11" paper. While 8"x 10-1/2' paper can be used in these storage containers, 10% of storage space therein is wasted.

(7) To the best of our knowledge, the vast majority of prior submissions have been on 8-1/2"x 11" paper. If §120.9 (b) means that master files must be converted to 8"x 10-1/2" paper "as if it were a portion of a petition" the task would be an impossible burden.

For the reasons stated above and probably additional complications not yet conceived, it is suggested that paper size requirement be deleted. Further, it is requested that double spacing be suggestive rather than obligatory or the requirement modified by "where practical." The re-typing of large amounts of available material now in single space does not appear to be a reasonable requisite for food additive petitions.

§121.50 (e) I.B.2.

Please note that comments made here under "I. Introduction" are equally applicable to the more detailed but comparable requirements in "II. Body of the petition."

Subparagraph I.B.2. of the Introduction requires "an estimate of the maximum as well as the average quantity of the food additive to be expected in the total daily diet." With respect to direct additives,

an average daily consumption can be calculated if total production and sale for the food use is known; the maximum daily consumption even in the case of direct additives depends upon percent of food consumed which contains the food additive, and assumes the additive is always present at a uniform level. In the case of incidental additives, estimation of average quantity of an additive in the diet is very difficult; estimation of maximum quantity is virtually impossible. Incidental additives enter the food via innumerable routes and any attempt to estimate anything but average daily consumption is an exercise in futility.

At the time of petitioning, even the average daily consumption will be little more than a guess with most direct or indirect additives because the petitioner usually has only a projected sale sufficient to justify economic production, which projection it may take years to achieve.

While we agree that efforts should be made to estimate dietary consumption of food additives, we submit that only averages are reasonable and that deviations from average are protected by the safety factor (usually 100) normally employed where limitation is deemed desirable. Accordingly, with respect to incidental additives, we recommend deletion of requirement that maximum dietary levels be estimated.

The reference to maximum amounts of a food additive in the daily diet appears in three other places in the proposed regulation, namely, in I.B.5; II.B.and II.B.2. Our comments are intended to apply equally to these other references.

§121.50 (e) I.B.5.

This subparagraph again includes "the maximum safe level in the diet of the consumer" presumably as an estimate derived from no-effect levels in toxicological investigation on laboratory animals.

Near the end of this subsection the term "any comparable substance" is indefinite because it does not state the basis of comparability. Thus, many substances are comparable from the point of view of their effect in foods but not at all comparable from a toxicological or chemical viewpoint. To avoid confusion it is suggested that the words "and comparable substances" be deleted.

§121.50 (e) II.A.1.

It is suggested that the title "Identity" of this subsection is poorly descriptive of the material contained therein and that "Description of product and process" would be a more suitable title. Further, it is suggested that the terms "complete quantitative composition" (b.i.), "food grade specifications" (b.v.) and "reproducibility of the additive" (b.v.i.) all mean substantially the same thing and would be best covered by the title "food additive specification".

Also b.v. of this subsection appears to assume that additive has been manufactured for some time, whereas in fact "production" batches may not yet be available at the time of petitioning. Consequently, product specifications are petitioner's best estimate of quality he can meet in plant practice based on laboratory or pilot plant experience. It is suggested that the word "production" be deleted.

With respect to manufacturing process (a.iv.) it is suggested that only raw materials and their specifications be required. Analytical techniques as applied to raw materials are generally well known and are not vital to the production of a food additive. The important consideration is the final product specification and validation of the analytical methods used here.

For your consideration a redraft of subsection II.A. which we believe covers the essential information required for both direct and indirect additives is appended.

§121.50 (e) II.B.2.a.vi.

Methods for determining molecular weight distribution are generally complex and difficult to reproduce. We submit that extractive limitations for polymeric materials in selected solvents adequately reflect low molecular weight fractions which may be suspect toxicologically and that molecular weight distribution adds little to the appraisal of safety. Deletion of this requirement is suggested.

§121.50 (e) II.B.2.b.iii.

Under this subsection, complete and detailed production and processing information is required for every petition as a matter ofroutine. If a regulation for a food packaging product establishes an identification specification and a safe limit for extractables, we question the relevance or need for such detailed information about the manufacturing process. We point out that to require a manufacturer to file this information and commit to produce a food packaging or processing

material exactly as described therein imposes an inequitable burden as opposed to his competitor. Once a regulation issues, any producer can manufacture the food packaging material provided the products meets the regulatory product identification specification and the end test solubility limits, etc., specified therein. While the competitive manufacturer must, of course, adhere to good manufacturing practice, nonetheless he has complete flexibility in adjusting his process as best suits his technical needs. Yet the petitioner is bound by all the representations mentioned in the petition, and for each change presumably a new petition would have to be filed. If the filing of such information is not essential for the competitive manufacturer's production of a safe food packaging or processing material, we fail to see the relevance or need of requiring that a petitioner file such information as a matter of routine. We point out that with respect to drugs, it is FDA's position that any new manufacturer of a new drug subject to a new drug application must file before commencing production and obtain approval of a supplemental new drug application covering, among other things, the manufacturer's production and quality control procedures. Yet the Food Additives Amendment does not impose such a requirement on a competing manufacturer, the only requirement being that the product involved be produced in accordance with good manufacturing practice and meet whatever specifications, extractive limits, etc., that might be set by FDA's regulation. The net effect of such a requirement is that the petitioner who has developed his new facet of food technology may be severely disadvantaged over

his competitor with no appreciative benefit to the public health or public interest. We believe that the structure of §409 (b) of the Act, which details the requirements for a petition, supports the argument that production process information should be required only in special situations and not as a matter of routine.

In this regard, §409 (b) (2), subsections A through E thereof, lists the basic statutory requirements of data that must be included in a petition. No reference is made to production process information. A separate subsection of §409 (b), namely (b) (3), deals with the problem of supplying, upon request of the Secretary, "a full description of the methods used in and the facilities and controls used for the production of such additive." Thus, we believe it was the intent of Congress to provide that the Secretary have the right to require such information where relevant because of special circumstances, but not merely as a matter of routine in every petition. Otherwise, a separate section (b)(3) would be meaningless since the requirement of production process information would have been listed in subsection (b) (2) of §409.

With respect to the specific wording of this paragraph, it is presumed that "adjuvants" referred to therein refers only to such adjuvants as are incorporated in the basic polymer polymerization and not to adjuvants in a resin formulation. To our knowledge, the final resin formulation has not been the subject of a petition nor is it intended that they should be. Such formulations are comprised of the basic resin to which may be added GRAS materials, adjuvants listed under the basic resin

regulation and adjuvants otherwise permitted under Subpart F. as in regulations of the types represented by §121.2511, §121.2527 and §121.2541 as examples.

§121.50 (e) II.B.2.b.iv.

As in 121.50 (e) II.A.v. we submit that production batches are normally not available at the time of petitioning. Hence the word "production" should be deleted.

§121.50 (e) II.B.

Please note objection to "maximum" level of additive as developed in §121.50 (e) I.B.2 and 5 above.

§121.50 (e) II.B.1.

Whether a direct food additive remains unchanged or, if changed, the degree of such change may be difficult or impossible to determine with any degree of precision, particularly if added in small quantity. If the additive is not completely recoverable from the food, its fate may in part be postulated but development of any rigorous proof might be a major project. Accordingly, it is suggested that the phrase ". . . where reasonably practical" be inserted following the word "showing" in the first sentence.

The last sentence of this paragraph requires specimens of all labels and labeling proposed. We would like to know whether this sentence is intended to limit petitioner strictly to labels presented with the petition and whether any change therein will require a new petition.

§121.50 (e) II.B.2.

Although migration data using actual and simulated foods will determine extent of transfer of a food additive in terms of milligrams per square inch of food contact surface under conditions of use, we submit that it will not provide information from which the maximum daily dietary intake can be calculated for reasons stated in §121.50 (e) I.B.2. above. Accordingly, comments there are equally applicable to this subsection.

§121.50 (e) II.D.2.

This subsection requires that in the case of the food additive needing a tolerance the regulatory method (analytical procedure) ". . . be satisfactory for application to the raw, processed, and/or finished food." While this requirement is presumably intended for direct additives or those substances incidentally present in a final product because of addition for functional use elsewhere in the production operation, we would like to point out that the extractive residue limitation (frequently 0.5 mg/in^2) in many regulations concerned with plastic packaging could be interpreted as a tolerance requiring that the regulatory method be applicable to the finished food. Accordingly, it is suggested that the requirement be limited as indicated.

§121.50 (f).

As stated under §121.9 (c) above we are firmly of the opinion that toxicology and analytical methods are entitled to protection as trade secrets except where

an enforcement action requires revelation. We believe that petitioner should have prior knowledge of intended release of any confidential information and that FDA has the obligation to show cause why such release is necessary to protect the public health. We are not unmindful of FDA's obligation to the public and believe FDA must use all information available in reaching conclusion concerning the public safety regardless of source. This does not require public release of data except in broad summary.

§121.51 Processing of food additive petitions

§121.51 (a) (1)

This subsection provides that "If the petition cannot be filed, two of the three copies of it will be returned to the petitioner." We believe that if the petition needs to be revised the petitioner would prefer to have the unacceptable version returned and completely destroyed . If the petition is administratively rejected, there is no need to retain a bulky document in FDA files. The cover letter required in §121.50 (d) provides official record that a petition was submitted, the name of the food additive and the proposed use.

§121.51 (b)

It is suggested that this subsection be revised so as to delete the words "or as appropriate."

Section 409 (b) (5) of the Food, Drug and Cosmetic Act clearly states that "notice of the regulation proposed by the petitioner shall be published in general terms by the secretary within thirty days after filing."

Congress has clearly not required the agency to specify in detail in a food additive proposal the specific claims made for the food additive. In the past, the agency has noticed human food additive proposals in the Federal Register on a broad general basis in accordance with the statutory authority. On the other hand, with respect to animal food additive petitions, the agency has set forth the proposal in great detail. It is suggested that human food additive proposals and animal food additive proposals should be treated equally, and both should be published in the Federal Register in general terms.

Publication of the details of a proposal (prior to approval) is an invitation for purchasers to use the food additive (particularly in animal feeds) for a use which has been proposed but not yet approved. The publishing of the proposal in general terms without reference to specific claims, would eliminate this possibility.

§121.51 (e)

If further information or sample is requested by FDA "a reasonable time in advance of 180 days, but is not submitted within such 180 days after filing the petition, the petition will be considered withdrawn without prejudice." It is suggested that "reasonable time in advance of 180 days" is too indefinite and that "180 days" implies that if added data are required the petitioner has no hope for a regulation within the 90 days provided by Section 409 (c) (2) of the Food, Drug

and Cosmetic Act and little hope of obtaining a regulation within the statutory limit of 180 days. While we would hope that request for sample and/or additional data be made within 45 days after date of filing a limit of 90 days would appear equitable. It must be recognized that the time required to provide information or sample may vary from days to months depending upon nature of the request. The petitioner should not be penalized by withdrawal of petition when, in fact, notice in advance of 180 days is not adequate to fill request.

§121.51 (d)

It is respectfully requested that petitioner be provided an opportunity to review language of a proposed regulation prior to publication in the Federal Register if it differs from that proposed by petitioner (§121.50(e)II.G.) and that this subsection be so revised.