September 22, 1967

DU PONT ANALYSIS OF
FDA PROPOSED MODIFICATIONS TO
PROCEDURAL FOOD ADDITIVE REGULATIONS
121.9 - FOOD ADDITIVE MASTER FILES
121.50 - CONTENT AND FORM OF FOOD ADDITIVE PETITIONS

121.9 - Food Additive Master Files

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 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 exeluding 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 120.50(f) or, at the very least, that 120.50(f) be revised to be consistent with 120.9(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

Our comments with respect to this proposed regulation are made in the same sequence as the proposed regulatory text.

1. 121.50(a) - Under this section, any published information used in support of the petition shall be submitted in reprint form. In many cases, it is extremely difficult to obtain reprints, particularly if such reprints must be on 8" x 10-1/2" pages as would be required by proposed subsection (c) of this regulation. For this reason, we

would suggest that after the word "reprint" the words "or readable copy" be inserted.

2. 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."

3. Section 121.50(b), dealing with incorporation by reference of previous submissions, permits same 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 and 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. For example, detailed toxicological studies submitted in early 1950 which led to a prior sanction or approval could still be valid and, indeed, are in many cases. Data in food additive petitions filed since the effective date of the Food Additives Amendment could still be valid in 1969. Yet according to the regulation, unless such data were now incorporated into a food additive Master File, presumably in the form required by 121.50 [see 121.9(b)], it could no longer be referred to regardless of the validity after 10 years. In addition, there are many situations where, for one reason or another, copies of studies have been misplaced though there is a record that they were submitted to the FDA. Thus FDA may have the only copy of the raw data, and to automatically conclude that such studies after 10 years are no longer reliable would create great hardship.

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 a 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."

4. Subsection (c) of 121.50 prescribes the physical form and size of the paper which must be used in connection with petitions. It is often desirable for the sake of completeness to include past studies in a petition rather than incorporate same by reference. According to subsection (c), all such studies would have to be retyped or reproduced on 8" x 10-1/2" paper and comply with express margin requirements. While this may be a federal government standard, we point out that 8" x 10-1/2" paper size has not been and is not now generally used by industry. Such a

specification would require the stocking and use of special size paper solely for use in FDA petitions. In addition, many petitions now in the process of preparation contain numerous detailed analytical and toxicological reports prepared on paper sizes at variance with the proposed 8" x 10-1/2" standard. Accordingly, thousands of pages would have to be needlessly retyped. Furthermore, reprints of publications may be of many different sizes. For these reasons, we would recommend that the paper size requirement in subsection (c) be deleted or at least be revised to exclude reprints and all reports previously filed or not as yet unfiled which have been prepared or published prior to the effective date of this proposed regulation. In this regard, 120.9(b) requires with respect to Master Files that the "material be arranged and indexed by page numbers as if it were a portion of a petition." Does this mean, in connection with now establishing a Master File, that all previous submissions that may go back 20 years or more must be refiled in the form and on paper size specified in 121.50? If so, this is an unrealistic objective and an impossible burden.

5. 121.50(e) - Petition Form. (Our comments applicable to I. Introduction are equally applicable to the more detailed but comparable requirements in Part 2, Body of the Petition.)

6. 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 incidental additives, whether food packaging or processing materials or components thereof, one might be able to arrive at an estimated average quantity of the food additive that may be expected in the total daily diet. Even this would be at best a relatively meaningless number. However, it would be virtually impossible to develop any kind of meaningful maximum quantity estimate since food packaging and processing materials as opposed to direct additives for the most part cover across-the-board as opposed to limited or restricted food contact. For example, with respect to an intentional additive to a food used under specific dietary circumstances such as with ulcer or low sodium diets, it may be possible to estimate a maximum level of consumption because the specific food use of the additive is usually clearly defined. Such a numbers game is virtually impossible with most incidental additives which might come in contact with any or all types of foods under a variety of industrial processing and packaging use conditions. Accordingly, with respect to incidental additives, we recommend deletion of any "maximum dietary levels."

The reference to estimates of the maximum amount of the daily diet appears in three other places in the proposed regulation, and our comments here apply equally to these other references which are in I.B.5, II.B and II.B.2.

7. Subsection 5 of the summary relating to toxicology requires "highlights of the studies" and states further that the highlights shall include "the no-effect levels found in the several species of test animals and the maximum safe level in the diet of the consumer." We believe this sentence should be revised to read as follows: "The highlights shall include the no-effect levels, if any, found in the several species of test animals and the maximum safe level in the daily diet of the consumer." Finally, in determining margins of safety, this subsection requires that the petitioner must take "into consideration previously approved food additive uses for the substance and any comparable substance." In many instances, a petitioner would not know, particularly with respect to prior sanctions or unpublished GRAS rulings, all approved food additive uses. In addition, regulations may issue without any specific limit on use; the only limit being good manufacturing practice. In all such cases, the petitioner would not be in a position to make any

reliable evaluations concerning the dietary impact of matters as to which he has no knowledge. Moreover, there is no definition of the words "comparable substance" provided in the regulation. From the toxicological point of view, the word is essentially meaningless since any chemical difference could lead to substantially different toxicological conclusions. Thus, a petitioner would be in no position to make a judgment as to what is a comparable substance. Furthermore, we point out there is no similar requirement as to previously approved food additive substances or comparable substance in Section E - Safety.

8. The requirement of a molecular weight distribution in II.A. 2(a)(vi) for incidental additives is difficult to comply with and, in any case, unnecessary. There is no established method of determining molecular weight distribution, and the techniques that have been developed are not only complex and detailed, but the results are hard to reproduce. We submit that the essential element of safety in connection with the incidental additive is the total safe extractive limit for any particular packaging or processing material or component thereof established in a regulation. Assuming that molecular weight variations may affect solubility and total extractives, the product involved for which an identification specification would also have been established would

have to meet the total extractives or solubility limits set by the regulation. Thus, variations in molecular weight distribution which might result in a product having higher extractive or solubility limits would also bar such product from the market. As a result, the question is self-policing. Accordingly, in our opinion, molecular weight distribution adds nothing to the appraisal of safety of an established level of extractables, and we would recommend deletion of this requirement.

9. Under II.A.2(b)(iii), complete and detailed production and processing information is required for every petition as a matter of routine. 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.

10. II A.2(b)(iv) requires data from a suitable number of production batches of food contact surfaces. Information of this type is normally not available since a new food packaging product cannot be produced or sold at a commercial

level until such time as an appropriate food additive regulation issues. Possibly this difficulty could be resolved by requiring a petitioner to submit, within a fixed period subsequent to issuance of a regulation or commencement of commercial production, representative production batches of the food contact surfaces involved for evaluation against the regulatory end test. If the petitioner or his customers could not in commercial production meet the regulatory requirement, the regulation could be withdrawn. For this reason, we would suggest the deletion of the last sentence in II.B.2(b)(iv) beginning with the word "Data" and, further, that II.B.2 (b)(v) be revised to read merely, "Anticipated range of variability of the food contact surface."

11. Subsection II.B.2 requires a "description of the conditions of use in detail with respect to the individual food or classes of food contacted."

This type of data is relevant only where restricted use applications are regulated. In normal food packaging or processing regulations where all types of foods might be expected to come into contact with the food contact surface, it would be impossible to provide in any meaningful detail a listing of use conditions with respect to individual foods or classes of foods. Moreover, with respect

to unrestricted food packaging or processing applications, a petitioner could at best only provide a general list of the types of food where, in its opinion, use of the food packaging or processing material involved might be employed. Even this kind of statement would hardly be meaningful. Similarly, any estimate of the maximum quantity of the food additive that might be expected in the total daily diet of the consumer would be virtually impossible to arrive at (see previous comments with respect to I.B.2).

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