DEPARTMENT OF HEALTH & HUMAN SERVICES

MAY 8 2001

Food and Drug Administration
Rockville MD 20857

**REGISTERED MAIL**
**RETURN RECEIPT REQUESTED**

Rodner Winget, Ph.D.
Director of Research
BioMarine Technologies, Inc.
13265 89th Ave S, Rt. 3
Renton, WA 98055

Re: Docket No. 91A-0222/AP1

Dear Dr. Winget:

It has been brought to my attention that, according to the records of the Dockets Management Branch of the Food and Drug Administration (FDA), the request for advisory opinion referenced above, submitted by you on May, 8, 1991, is still formally unresolved. Your request was in regard to the use of certain solvents[1] during the extraction procedure for obtaining eicosapentaenoic acid (EPA). I apologize for how long it has taken to get back to you on this. To resolve this as expeditiously as possible, I am writing so that you might know the agency's likely position were it to issue a formal opinion on this matter.

You explained that you are planning to use the EPA obtained during the extraction process in EPA-containing oils that are potentially to be manufactured into pharmaceutical products by another firm. You specifically requested that the agency advise on the use of each solvent listed in your petition during the extraction process, including the maximum acceptable levels of the solvents as residuals in an ingested or topically applied pharmaceutical product. You also asked for an advisory opinion about the use of iron, sodium borate, and silver nitrate in your column packing material.

An advisory opinion cannot reasonably be given on the matter involved (21 CFR 10.85(a)(2)(ii); see enclosed). The Center for Drug Evaluation and Research generally makes specific recommendations about scientific or medical issues related to a pharmaceutical product only when the finished drug product is proposed for investigational use (i.e., human testing) or for marketing. This generally occurs when a company has completed its preliminary formulation and development of a drug product, and has submitted to the agency an investigational new drug application (IND) or, if they are proposing the drug product for immediate marketing, a new drug application (NDA).

[1] These solvents included: ethanol (96:4 water), hexane (79:21 etbanoi), chloroform (93:21 ethanol), methylenechloride(95:5 ethanol), acetonitrile (45:57 ethanol), methylethylketone(66:40 ethanol), isopropanol ((22:78 hexane), methanol (27:73 hexane), methylisobutylketone (76:24 water), ethyl ether (99:1 water), formic acid (77.5:22.5 water), acetic acid (3:97 water), potassium phosphate (solubilized in water), and ammonia solution (evaporated).

91A-0222

CET/

Rodger Winget, Ph. D.

Under both these applications an applicant is required to submit a wide range of information about the drug product, including information about the active and inactive ingredients, impurities, and manufacturing processes. This information gives the agency the ability to review thoroughly the safety of the completed drug product, and to make knowledgeable recommendations to the applicant about further development. The product as described in your request is at an early stage of development and the agency has very little information about it. As a practical matter, therefore, it is not really possible for the agency to make a reasoned judgment about appropriate impurities limits for the specified substances in a finished dosage form containing your product, or other regulatory decisions relating specifically to your product.

Also, your request relates to a particular product or products and not to a policy issue of broad applicability (21 CFR 10.85(a)(2)(iv)). Advisory opinions issued by the agency become matters of public record that are available to the industry and public, and may be relied upon as formal statements of agency policy (see 21 CFR 10.85(e)). One of the main purposes of expending the resources necessary to issue an advisory opinion is to provide the public and industry with the agency's position on a matter that has wide applicability. The agency is not aware of other members of the public or industry that would be assisted or benefited by issuing a formal agency response to the questions presented in your petition.

You might be interested in the enclosed guidance document, entitled "Q3c Impurities: Residual Solvents." It provides recommendations on maximum daily exposure limits in drug substances and drug products for certain residual solvents, including many of the solvents listed in your petition. You may find information in the guidance to be useful in your pharmaceutical development efforts.

As I said above, the opinions in this letter represent the agency's likely response were it to issue a formal opinion. If you wish to prolong this proceeding, please respond to Docket No. 91A-0222/AP1, Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville MD 20852. If we do not receive a written response from you within 30 days, a copy of this letter will be filed in the docket with instructions that the request be considered to have been voluntarily withdrawn. If you have any questions, please contact me at 301-594-2041.

Sincerely yours,

Dave Read
Supervisory Regulatory Counsel
Regulatory Policy Staff (HFD-7)
Center for Drug Evaluation and Research

Enclosures

| Toxicological profile | NTIS order No. | CAS No. |
|---|---|---|
| 1. Di–N–OCTYLPHTHALATE | PB98–101033 | 000117–84–0 |
| 2. ETHYLENE GLYCOL/ | PB98–101108 | 000107-21-1 |
| PROPYLENE GLYCOL | | 000057–55–6 |
| 3. HEXACHLOROETHANE | PB98–101041 | 000067-72-I |
| 4. HMX | PB98–101056 | 002691–41–0 |
| 5. HYDRAULIC FLUIDS | PB98–101066 | VARIOUS |
| 6. HYDRAZINES | PB98–101025 | 000302-01-2 |
| 1,1-DIMETHYLHYDRAZINE | | 000057-14-7 |
| 1,2-DIMETHYLHYDRAZINE | | 000540–73–8 |
| DIMETHYLHYDRAZINE | | 030260-66-3 |
| 7. MINERAL-BASED CRANKCASE OIL | PB98–101066 | 008002–05–9 |
| 8. TITANIUM TETRACHLORIDE | PB98–101074 | 007550–45–0 |
| 9. WHITE PHOSPHORUS | PB98–101082 | 007723-14-o |

Dated: December 17. 1997.

**Georgi Jones,**

*Director, Office of Policy and External Affairs, Agency for Toxic Substances and* Disease *Registry.*

[FR Doc. 97-33508 Filed 12-23-97: 8:45 am]

BILLING CODE 4163-70-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Centers for Disease Control and Prevention

### National Vaccine Advisory Committee (NVAC), Subcommittee on Future Vaccines, Subcommittee on Immunization Coverage, and Subcommittee on Vaccine Safety: Meetings

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announces the following Federal advisory committee meetings.

Name: National Vaccine Advisory Committee (NVAC).

*Times and Dates:* 9 a.m.-2 p.m.. January 12, 1998. 8:30 a.m.–1:15 p.m., January 13, 1998.

*Place:* Hubert H. Humphrey Building, Room 800.200 Independence Avenue.' SW. Washington, DC 20201.

*Status:* Open to the public, limited only by the space available.

Notice: In the interest of security, the Department has instituted stringent procedures for. entrance *to the* Hubert H. Humphrey Building by non-government employees. Thus. persons without a government identification card should plan to arrive at the building each day either between 8 and 8:30 a.m. or 12:30 and 1 p.m. so they can be escorted to the meeting. Entrance to the meeting at other times during the day cannot be assured.

*Purpose:* This committee advises and makes recommendations to the Director of the National Vaccine Program on matters related to the Program responsibilities.

*Matters To Be Discussed:* Agenda items will include updates on the National Vaccine Program Office (NVPO) activities; the National Vaccine Plan and NVAC's role in defining priorities for action; unmet needs funding-past, present and future; adult immunization: report of the Workgroup; use of non-traditional sites for adult immunization: influenza: a growing need for pandemic preparedness: and a discussion on vaccines for international travel.

In addition, there will be updates on welfare reform and effects on immunization: moving towards a Department of Health and Human Services' vaccine safety action plan; work group on philosophical exemptions—final report: the presidential initiative on immunization registries; global use of critically needed vaccines-strategies to consider. There will be reports from the Subcommittee on Immunization Coverage, Subcommittee on Future Vaccines, and Subcommittee on Vaccine Safety.

*Name:* Subcommittee on Immunization Coverage.

*Time and Date: 2* p.m.-5 p.m., January 12. 1998.

Place: Hubert H. Humphrey Building, Room 423A, 200 Independence Avenue, SW. Washington, DC 20201.

*Status:* Open to the public. limited only by the space available.

*Purpose:* This subcommittee will identify and propose solutions that provide a multifaceted and holistic approach to reducing barriers that result in low immunization coverage for children.

*Matters To Be Discussed: This* subcommittee will hold a discussion on the review of recommendations from the document, "Strategies to Sustain Immunization Coverage," and the finalization of those recommendations.

Name: Subcommittee on Future Vaccines.

*Time and Date: 2* p.m.-5 p.m., January 12. 1998.

Place: Hubert H. Humphrey Building, Room 405A, 200 Independence Avenue, SW, Washington, DC 20201.

*Status:* Open to the public, limited only by the space available,

*Purpose:* The Subcommittee on Future Vaccines will develop policy options and guide national activities which will lead to accelerated development. licensure, and best use of new vaccines in the simplest: possible immunization schedules.

*Matters* To *Be Discussed:* This subcommittee will hold discussions regarding the continued evaluation of methods to remove barriers to development, licensure and use of safe and effective new vaccines; combination vaccines. strategic options; and defining future vaccines policy issues for travelers' vaccines.

Name: Subcommittee on Vaccine Safety.

Time and Date: 2 p.m.-5 p.m.. January 12, 1998.

*Place:* Hubert H. Humphrey Building. Room 800,200 Independence Avenue, SW, Washington, DC 20201.

*Status:* Open to the public, limited only by the space available.

*Purpose:* This subcommittee will review issues relevant to vaccine safety and adverse reactions to vaccines.

*Matters To Be Discussed: This* subcommittee will hold discussions regardingits goals: a report from the Task Force on Safer Childhood Vaccines: a project report on benefit-risk communication curriculum development: and agenda items for the next meeting.

Agenda items are subject to change as priorities dictate.

*Contact Person for More Information:* Felecia D. Pearson. Committee Management Specialist. NVPO, CDC, 1600 Clifton Road, NE. M/S D50, Atlanta, Georgia 30333. telephone 404/639–4450.

Dated: December 19. 1997.

Carolyn J. Russell,

*Director, Management Analysis and Services Office, Centers for Disease Control and Prevention (CDC).*

[FR Doc. 97-33666 Filed 12-23-97: 8:45 am]

BILLING CODE 4163–18–P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 97D–0148]**

### International Conference on Harmonisation; Guidance on Impurities: Residual Solvents

**AGENCY:** Food and Drug Administration. HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is publishing a guidance entitled "Q3C Impurities:

Residual Solvents." The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient, and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms.

**DATES:** Effective December 24. 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. l-23, Rockville, MD 20857. Copies of the guidance are available from the Drug Information Branch (HFD-210). Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville. MD 20857, 301-827-4573.

**FOR FURTHER INFORMATION CONTACT:**

Regarding the guidance: John J. Gibbs, Center for Drug Evaluation and Research (HFD-820). Food and Drug Administration; 5600 Fishers Lane., Rockville, MD 20857, 301-827-6430.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

**SUPPLEMENTARY INFORMATION:** In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed: to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions:. The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) , FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat. which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) .

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA. as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of May 2, 1997 (62 FR 24302), FDA published a draft tripartite guideline entitled "Impurities: Residual Solvents" (Q3C). The notice gave interested persons an opportunity to submit comments by June 16.1997.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed. by the three participating regulatory agencies on July 17, 1997.

In accordance with FDA's Good Guidance Practices (62 FR 896 1, February 27. 1997), this document has been designated a guidance, rather than a guideline

Residual solvents in pharmaceuticals are organic volatile chemicals that are used or produced in the synthesis of drug substances or excipients, or in the preparation of drug products. They are not completely removed by practical manufacturing techniques. The guidance recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The guidance recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. The guidance applies to residual solvents in drug substances, excipients, and drug products, and to all dosage forms and routes of administration. The guidance does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

This guidance represents the agency's current thinking on acceptable amounts of residual solvents in pharmaceuticals. It does not create, or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations. or both.

As with all of FDA's guidances, the public is encouraged to submit written comments with new data or other new information pertinent to this guidance. The comments in the docket will be periodically reviewed, and, where appropriate. the guidance will be amended. The public will be notified of any such amendments through a notice in the **Federal Register.**

Interested persons may, at any time, submit written comments on the guidance to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet (http://www.fda.gov/cder/guidance.htm).

The text of the guidance follows:

**Q3C Impurities: Residual Solvents[1]**

**1. Introduction**

The objective of this guidance is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guidance recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents,

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity. and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guidance does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices. or other quality-based requirements. Drug products should contain

[1] This guidance represents the agency's current thinking on acceptable amounts of residual solvents in pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public, An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 1) should be avoided in the production of drug substances. excipients. or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2. Table 2) should be limited in order to protect patients from potential adverse effects. Ideally. less toxic solvents (Class 3, Table 3) should be used where practical. The complete list of solvents included in this guidance is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the lists. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety date becomes available. Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guidance or the concept of qualification of impurities as expressed in the guidance for drug substance (Q3A, impurities in New Drug Substances) or drug product (Q3B, Impurities in New Drug Products), or all three guidances.

2. Scope of the Guidance

Residual solvents in drug substances, excipients. and drug products are within the scope of this guidance. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only considered necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products. Aithough manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. if the calculation results in a level equal to or below that recommended in this guidance. no testing of the drug product for residual solvents need be considered. If. however, the calculated level is above the recommended level. the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guidance does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guidance applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short-term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis.

See Appendix 2 of this document for additional background information related to residual solvents.

3. General Principles

*3.1 Classification of Residual Solvents by Risk Assessment*

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guidance as a pharmaceutically acceptable intake of residual solvents to avoidconfusion of differing values for ADI's of the same substance.

Residual solvents assessed in this guidance are fisted in Appendix 1 by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

*Class* I *solvents:* Solvents to be avoided— Known human carcinogens; strongly suspected human carcinogens. and environmental hazards.

*Class* 2 *solvents:* Solvents to be limited— Nongenotoxic animal carcinogens or possible causative agent; of other irreversible toxicity such as neurotoxicity or teratogenicity.

Solvents suspected of other significant but reversible toxicities.

*Class* 3 *solvents:* Solvents with low toxic potential—

Solvents with low toxic potential to man: no health-based exposure limit is needed. Class 3 solvents have PDE's of 50 milligrams (mg) or more per day.

*3.2 Methods for Establishing Exposure Limits*

The method used to establish permitted daily exposures for residual solvents is presented in Appendix 31 Summaries of the toxicity data that were used to establish limits are published in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997.

*3.3 Options for Describing Limits of Class 2* Solvents

Two options are available when setting limits for Class 2 solvents.

*Option* 1: The concentration limits in parts per million (ppm) stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 grams (g) administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances. excipients. or products. Therefore, this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1. then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day should be considered under Option 2.

*Option 2:* It is not considered necessary for each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1) , as shown in Option 1 in the previous paragraph,, to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process and the limits should reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product, The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the use of Option 1 and Option 2 applied to acetonitrile in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day: thus, the Option 1 limit is 410 ppm. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

| Component | Amount in formulation | Acetonitrile content | Daily exposure |
|---|---|---|---|
| Drug substance | 0.3 g | 800 ppm | *0.24* mg |
| Excipient 1 | *0.9* g | 400 ppm | *0.36* mg |
| Excipient 2 | *3.8* g | 800 ppm | *3.04* mg |
| Drug product | 5.0 g | 728 ppm | *3.64* mg |

Excipient 1 meets the Option 1 limit, but-' the drug substance, excipient 2. and drug product do not meet the Option 1 limit. Nevertheless. the product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guidance.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The, composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

| Component | Amount in formulation | Acetonitrile content | Daily exposure |
|---|---|---|---|
| Drug substance | 0.3 g | 800 ppm | 0.24 mg |
| Excipient 1 | 0.9 g | 2,000 ppm | 1.80 mg |
| Excipient 2 | 3.8 g | 800 ppm | 3.04 mg |
| Drug product | 5.0 g | 7,016 ppm | 5.08 mg |

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced. during formulation to the allowed limit. then the manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product. If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guidance value, and provide a risk-benefit analysis to support allowing the product to be utilized with residual solvent at a higher level.

### 3.4 *Analytical Procedures*

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents asdescribed in the pharmacopoeias should be 'used, if feasible, Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a nonspecific method such as loss on drying may 'be used.

Validation of methods for residual solvents should conform to ICH guidances "Q2A Text oh Validation of Analytical Procedures" and "Q2B Validation of Analytical Procedures: Methodology."

### *3.5 Reporting Levels of Residual Solvents*

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or drug substances in order to meet the criteria of this guidance. The following statements are given as acceptable examples of the information that could be provided from a supplier of excipients or drug substances to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5 percent.
- Only Class 2 solvents X, Y. * * * are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y. * * * .)
- Only Class 2 solvents X, Y. * * * and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 percent.

If Class 1 solvents are likely to be present. they should be identified and quantified.

"Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5 percent, respectively, they should be identified and quantified.

## 4. Limits of Residual Solvents

### *4.1 Solvents to Be Avoided*

Solvents in Class 1 should not be employed in the manufacture of drug substances. excipients. and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. The solvent 1.1, 1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1,500 ppm is based on a review of the safety data.

TABLE 1 .—CLASS 1 SOLVENTS IN PHARMACEUTICAL PRODUCTS (SOLVENTS THAT SHOULD BE AVOIDED)

| Solvent | Concentration limit (ppm) | Concern |
|---|---|---|
| Benzene | 2 | Carcinogen |
| Carbon tetrachloride | 4 | Toxic and environmental hazard |
| 1,2-Dichloroethane | 5 | Toxic |
| 1,1-Dichloroethene | 8 | Toxic |
| 1,1,1-Trichloroethane | 1.500 | Environmental hazard |

### *4.2 Solvents to Be Limited*

Solvents in Table 2 should be limited in pharmaceutical products because of their inherent toxicity. PDE's are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of &he validation of the method

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS

| Solvent | POE(mg/day) | Concentration limit (ppm) |
|---|---|---|
| Acetonitrile | 4.1 | 410 |
| Chlorobenzene | 3.6 | 360 |
| Chloroform | 9.6 | 60 |
| Cydohexane | 38.8 | 3,880 |
| 1,2-Dichloroethene | 18.7 | 1,870 |

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS—Continued

| Solvent | PDE (mg/day) | Concentration limit (ppm) |
|---|---|---|
| Dichloromethane | 6.0 | 600 |
| 1,2-Dimethoxyethane | 1.0 | 100 |
| N,N-Dimethylacetamide | 70.9 | 1,090 |
| N,N-Dimethylformamide | 8.8 | 880 |
| 1,4-Dioxane | 3.8 | 380 |
| 2-Ethoxyethanol | 1.6 | 160 |
| Ethyleneglycol | 6.2 | 620 |
| F ormamide | 2.2 | 220 |
| Hexane | 2.9 | 290 |
| Methanol | 30.0 | 3.000 |
| 2-Methoxyethanol | 0.5 | 50 |
| Methylbutyl ketone | 0.5 | 50 |
| Methylcyclohexane | 11.8 | 1,180 |
| N-Methylpyrrolidone | 48.4 | 4,840 |
| Nitromethane | 0.5 | 50 |
| Pyridina | 2.0 | 200 |
| Sulfolane | 1.6 | 160 |
| Tetralin | 1.0 | 100 |
| Toluene | 8.9 | 890 |
| 1,1,2-Trichloroethene | 0.8 | 80 |
| Xylene[1] | 21.7 | 2,170 |

[1] Usually 69% m-xylene. 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

*4.3 Solvents with Low Toxic Potential*

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute, or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

TABLE 3.—CLASS 3 SOLVENTS WHICH SHOULD BE LIMITED BY GMP OR OTHER QUALITY-BASED REQUIREMENTS

| | |
|---|---|
| Acetic acid | Heptane |
| Acetone | Isobutyl acetate |
| Anisole | Isopropyl acetate |
| 1-Butanol | Methylacetate |
| 2-Butanol | 3-Methyl-1-butanol |
| Butyl acetate | Methylethyl k&one |
| *tert*-Butylmethyl ether | Methylisobutyl ketone |
| Cumene | 2-Methyl–1-propanol |
| Dimethyl sulfoxide | Pentane |
| Ethanol | 1-Pentanol |
| Ethyl acetate | 1-Propanol |
| Ethyl ether | 2-Propanol |
| Ethyl formate | Propylacetate |
| Formic acid | Tetrahydrofuran |

*4.4 Solvents for Which No Adequate Toxicological Data Were Found*

The following solvents (Table 4) may also be of interest to manufacturers of excipients, drug substances. or drug products. However. no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

TABLE 4.—SOLVENTS FOR WHICH NO ADEQUATE TOXICOLOGICAL DATA WERE FOUND

| | |
|---|---|
| 1 ,I-Diethoxypropane | Methylisopropyl ketone |
| 1,1-Dimethoxymethane | Methyltetrahydrofuran |
| 2,2-Dimethoxypropane | Petroleum ether |
| Isooctane | Trichloroacetic acid |
| Isopropyl ether | Triflworoacetic acid |

## Glossary

*Genotoxic carcinogens: Carcinogens* that produce cancer by affecting genes or chromosomes.

*LOEL:* Abbreviation for lowest-observed effect level.

*Lowest-observed effect level: The* lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

*Modifying factor:* A factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data safely to humans.

*Neurotoxicity:* The ability of a substance to cause adverse affects *on the nervous* system.

*NOEL:* Abbreviation for no-observed-effect level.

*No-observed-effect* level: The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

*PDE:* Abbreviation for permitted daily exposure.

*Permitted daily exposure: The* maximum acceptable intake per day of residual solvent in pharmaceutical products.

*Reversible toxicity: The occurrence* of harmful effects that are caused by a substance and which disappear after exposure to the substance ends.

*Strongly suspected human carcinogen:* A substance for which there is no epidemiological evidence of carcinogenesis but there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

*Teratogenicity:* The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

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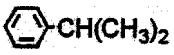
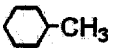
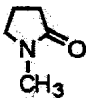
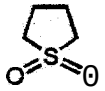
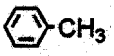
**Appendix 1.** List of Solvents Included in the Guidance

| Solvent | Other Names | Structure | Class |
|---|---|---|---|
| Acetic acid | Ethanoic acid | $CH_3COOH$ | Class 3 |
| Acetone | 2-Propanone<br>Propan-2-one | $CH_3COCH_3$ | Class 3 |
| Acetonitrile | | $CH_3CN$ | Class 2 |
| Anisole | Methoxybenzene |  | Class 3 |
| Benzene | Benzol |  | Class 1 |
| l-Butanol | n-Butyl alcohol<br>Butan-1-ol | $CH_3(CH_2)_3OH$ | Class 3 |
| 2-Butanol | sec-Butyl alcohol<br>Butan-2-ol | $CH_3CH_2CH(OH)CH_3$ | Class 3 |
| Butyl acetate | Acetic acid butyl ester | $CH_3COO(CH_2)_3CH_3$ | Class 3 |
| tert-Butylmethyl ether | 2-Methoxy-2-methyl-propane | $(CH_3)_3COCH_3$ | Class 3 |
| Carbon tetrachloride | Tetrachloromethane | $CCl_4$ | Class 1 |
| Chlorobenzene | |  | Class 2 |
| Chloroform | Trichloromethane | $CHCl_3$ | Class 2 |
| Cumene | Isopropylbenzene<br>(1-Methyl)ethylbenzene |  | Class 3 |
| Cyclohexane | Hexamethylene |  | Class 2 |
| 1,2-Dichloroethane | sym-Dichloroethane<br>Ethylene dichloride<br>Ethylene chloride | $CH_2ClCH_2Cl$ | Class.1 |

| | | | |
|---|---|---|---|
| 1,1-Dichloroethene | 1,1-Dichloroethylene<br>Vinylidene chloride | $H_2C=CCl_2$ | Class 1 |
| 1,2-Dichloroethene | 1,2-Dichloroethylene<br>Acetylene dichloride | ClHC=CHCl | Class 2 |
| Dichloromethane | Methylene chloride | $CH_2Cl_2$ | Class 2 |
| 1,2-Dimethoxyethane | Ethyleneglycol dimethyl ether<br>Monoglyme<br>Dimethyl Cellosolve | $H_3COCH_2CH_2OCH_3$ | Class 2 |
| N,N-Dimethylacetamide | DMA | $CH_3CON(CH_3)_2$ | Class 2 |
| N,N-Dimethylformamide | DMF | $HCON(CH_3)_2$ | Class 2 |
| Dimethyl sulfoxide | Methylsulfinylmethane<br>Methyl sulfoxide<br>DMSO | $(CH_3)_2SO$ | Class 3 |
| 1,4-Dioxane | p-Dioxane<br>[1,4]Dioxane |  | Class 2 |
| Ethanol | Ethyl alcohol | $CH_3CH_2OH$ | Class 3 |
| 2-Ethoxyethanol | Cellosolve | $CH_3CH_2OCH_2CH_2OH$ | Class 2 |
| Ethyl acetate | Acetic acid ethyl ester | $CH_3COOCH_2CH_3$ | Class 3 |
| Ethyleneglycol | 1,2-Dihydroxyethane<br>1,2-Ethanediol | $HOCH_2CH_2OH$ | Class 2 |
| Ethyl ether | Diethyl ether<br>Ethoxyethane<br>1,1'-Oxybisethane | $CH_3CH_2OCH_2CH_3$ | Class 3 |
| Ethyl formate | Formic acid ethyl ester | $HCOOCH_2CH_3$ | Class 3 |
| Formamide | Methanamide | HCONH, | Class 2 |
| Formic acid | | HCOOH | Class 3 |

| | | | |
|---|---|---|---|
| Heptane | n-Heptane | $CH_3(CH_2)_5CH_3$ | Class 3 |
| Hexane | n-Hexane | $CH_3(CH_2)_4CH_3$ | Class 2 |
| Isobutyl acetate | Acetic acid isobutyl ester | $CH_3COOCH_2CH(CH_3)_2$ | Class 3 |
| Isopropyl acetate | Acetic acid isopropyl ester | $CH_3COOCH(CH_3)_2$ | Class 3 |
| Methanol | Methyl alcohol | $CH_3OH$ | Class 2 |
| 2-Methoxyethanol | Methyl Cellosolve | $CH_3OCH_2CH_2OH$ | Class 2 |
| Methyl acetate | Acetic acid methyl ester | $CH_3COOCH_3$ | Class 3 |
| 3-Methyl-1-butanol | Isoamyl alcohol<br>Isopentyl alcohol<br>3-Methylbutan-1-ol | $(CH_3)_2CHCH_2CH_2OH$ | Class 3 |
| Methylbutyl ketone | 2-Hexanone<br>Hexan-2-one | $CH_3(CH_2)_3COCH_3$ | Class 2 |
| Methylcyclohexane | Cyclohexylmethane |  | Class 2 |
| Methylethyl ketone | 2-Butanone<br>MEK<br>Butan-2-one | $CH_3CH_2COCH_3$ | Class 3 |
| Methylisobutyl ketone | 4-Methylpentan-2-one<br>4-Methyl-2-pentanone<br>MIBK | $CH_3COCH_2CH(CH_3)_2$ | Class 3 |
| 2-Methyl-1-propanol | Isobutyl alcohol<br>2-Methylpropan-1-ol | $(CH_3)_2CHCH_2OH$ | Class 3 |
| N-Methylpyrrolidone | 1-Methylpyrrolidin-2-one<br>1-Methyl-2-pyrrolidinone |  | Class 2 |
| Nitromethane | | $CH_3NO_2$ | Class 2 |
| Pentane | n-Pentane | $CH_3(CH_2)_3CH_3$ | Class 3 |

| | | | |
|---|---|---|---|
| 1-Pentanol | Amyl alcohol<br>Pentan-1-ol<br>Pentyl alcohol | $CH_3(CH_2)_3CH_2OH$ | Class 3 |
| 1-Propanol | Propan-1-ol<br>Propyl alcohol | $CH_3CH_2CH_2OH$ | Class 3 |
| 2-Propanol | Propan-2-01<br>Isopropyl alcohol | $(CH_3)_2CHOH$ | Class 3 |
| Propyl acetate | Acetic acid propyl ester | $CH_3COOCH_2CH_2CH_3$ | Class 3 |
| Pyridine | |  | Class 2 |
| Sulfolane | Tetrahydrothiophene l,l-dioxide |  | Class 2 |
| Tetrahydrofuran | Tetramethylene oxide<br>Oxacyclopentane |  | Class 3 |
| Tetralin | 1,2,3,4-Tetrahydro-naphthalene |  | Class 2 |
| Toluene | Methylbenzene |  | Class 2 |
| 1,1,1-Trichloroethane | Methylchloroform | $CH_3CCl_3$ | Class 1 |
| 1,1,2-Trichloroethene | Trichloroethene | $HClC=CCl_2$ | Class 2 |
| Xylene[1] | Dimethybenzene<br>Xylol |  | Class 2 |

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene,.

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## Appendix 2. Additional Background

### *A2.1 Environmental Regulation of Organic Volatile Solvents*

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and the Integrated Risk Information System (IRIS). The objectives of such groups as the IPCS, the U.S. Environmental Protection Agency (EPA), and FDA include the determination of acceptable exposure levels. The goal is protection of human health and maintenance of environmental integrity against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The methods involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable. shorter term study data can be used with modification of the approach such as use of larger safety factors. The approach described therein relates primarily to long-term or ***lifetime exposure of the general population*** in the ambient environment. i.e.. ambient air. food, drinking water, and other media.

### *AZ.2 Residual Solvents in Pharmaceuticals*

Exposure limits in this guidance are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. They are as follows:

(1) Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.

(2) The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to. reduce risk to human health,

(3) Residual solvents are unavoidable components in pharmaceutical production and will often be a part of drug products.

(4) Residual solvents should not exceed recommended levels except in exceptional circumstances.

(5) Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described. for example, by the Organization for Cooperation and Development, EPA, and the FDA Red Bdok.

## Appendix 3. Methods for Establishing Exposure Limits

The Gaylor-Kodell method of risk assessment (Gaylor, D. W.. and R. L.Kodell, "Linear interpolation Algorithm for Low Dose Assessment of Toxic Substance," ***Journal of Environmental Pathology and Toxicology,*** 4:305. 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 solvents could be determined with the use of a large safety factor (i.e., 10.000 to 100,000) with respect to the NOEL. Detection and quantitation of these solvents should be by state-of-the-art **analytical** techniques.

Acceptable exposure levels in this guidance for Class 2 solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals ***(Pharmacopeial Forum,*** Nov-Dee 1989). and the method 'adopted by IPCS for Assessing Human Health Risk of Chemicals (EHC 170, WHO, 1994). These methods are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA (Red Book) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values tabulated-in Section 4 of this document.

PDE is derived from the NOEL or the LOEL in the most relevant animal study as follows:

$$PDE = \frac{\text{NOEL x Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5} \quad (1)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans. are the same kind of "uncertainty factors" used in EHC (EHC 170, WHO. Geneva, 1994). and "modifying factors" or "safety factors" in ***Pharmacopeial Forum.*** The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species.

F1 = 5 for extrapolation from rats to humans.

F1 = 12 for extrapolation from mice to humans.

F1 = 2 for extmpolation from dogs to humans.

Fl = 2.5 for extrapolation from rabbits to humans.

F1 = 3 for extrapolation from monkeys to humans.

F1 = 10 for extrapolation from other animals to humans.

F1 takes into account the comparative surface area:body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$s = kM^{0.67} \quad (2)$$

in which M = body mass. and the constant k has been taken to be 10. The body weights used in the equation are those shown below in Table A3.1.

F2 = A factor of 10 to account for variability between individuals.

A factor of 10 is generally given for ail organic solvents. and 10 is used consistently in this guidance.

F3 = A variable factor to account for toxicity studies of short-term exposure.

F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits: 7 years for cats, dogs and monkeys).

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.

F3 = 2 for a B-month study in rodents, or a 3.5-year study in nonrodents.

F3 = 5 for a 3-month study in rodents, or a Z-year study in nonrodents.

F3 = 10 for studies of a shorter duration. In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study.

F4 = A factor that may be applied in cases of severe toxicity. e.g., nongenotoxic carcinogenic&y, neurotoxicity or teratogenicity. In studies of reproductive toxicity. the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity.

F4 = 5 for fetal toxicity without maternal toxicity.

F4 = 5 for a teratogenic effect with maternal toxicity.

F4 = 10 for a teratogenic effect without maternal toxicity.

F5 = A variable factor that may be applied if the no effect level was not established.

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in ***Pharmeuropa,*** Vol. 9. No. 1, Supplement. April 1997. page S24. The NOEL is calculated to be 50.7 mg $kg^{-1}$ $day^{-1}$. The PDE for acetonitriie in this study is calculated as foiiows:

$$PDE = \frac{50.7 \text{ mg kg}^{-1} \text{ day}^{-1} \times 50 \text{ kg}}{12 \times 10 \times 5 \times 1 \times 1} = 4.22 \text{ mg day}^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans.

F2 = 10 to account for differences between individual humans.

F3 = 5 because the duration of the study was only 13 weeks.

F4 = 1 because no severe toxicity was encountered.

F5 = 1 because the no effect level was determined.

TABLE A3.1—VALUES USED IN THE CALCULATIONS IN THIS DOCUMENT

| | | | |
|---|---|---|---|
| Rat body weight | 425 g | Mouse respiratory volume | 43 liter (L)/day |
| Pregnant rat body weight | 330 g | Rabbit respiratory volume | 1,440 L/day |
| Mouse body weight | 28 g | Guinea pig respiratory volume | 430 Uday |
| Pregnant mouse body weight | 30 g | Human respiratory volume | 28,800 L/day |
| Guinea pig body weight | 500 g | Dog respiratory volume | 9,000 Uday |
| Rhesus monkey body weight | 2.5 kg | Monkey respiratory volume | 1,150 L/day |
| Rabbit body weight (pregnant or not) | 4 kg | Mouse water consumption | 5 milliliter(mL)/day |
| Beagle dog body weight | 11.5 kg | Rat water consumption | 30 mL/day |
| Rat respiratory volume | 290 L/day | Rat food consumption | 30 g/day |

The equation for an ideal gas, PV = nRT, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/cubic meter ($m^3$). Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa*, Vol. 9. No. 1, Supplement, April 1997. page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6}\ \text{atm} \times 153840\ \text{mg mol}^{-1}}{0.082\ \text{L atm K}^{-1}\ \text{mol}^{-1} \times 2911\ \text{K}} = \frac{46.15\ \text{mg}}{24.45\ \text{L}} = 1.89\ \text{mg/L}$$

The relationship 1000 L = 1 $m^3$ is used to *convert to* mg/$m^3$.

Dated: December 16. 1997.

William K. Hubbard,

*Associate Commissioner for Policy Coordination.*

[FR Doc. 97-33639 Filed 12-23-97: 8:45 am]

BILLING CODE 41W-OI-F

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Health Care Financing Administration

**[Form #HCFA–R–224]**

### Emergency Clearance: Public Information Collection Requirements Submitted to the Office of Management and Budget (OMB)

In compliance with the requirement of section 3506(c) (2) (A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services (DHSS), has submitted to the Office of Management and Budget (OMB) the following request for Emergency review. We are requesting an emergency review because the collection of this 'information is needed prior to the expiration of the normal time limits under OMB's regulations at 5 CFR, Part 1320. The Agency cannot reasonably comply with the normal clearance procedures because of a statutory deadline imposed by section 1853(a)(3) of the Balanced Budget Act of 1997. Without this information, HCFA would not be able to properly implement the requirements set forth in the statute.

HCFA is requesting OMB review and approval of this collection by 12/31/97, with a 180-day approval period. Written comments and recommendations will be accepted from the public if received by the individual designated below, by 12/29/97.

During this 180-day period HCFA will pursue OMB clearance of this collection as stipulated by 5 CFR 1320.5.

*Type of Information Collection Request: New* collection:

***Title of Information Collection:*** Collection of Managed Care Data Using the Uniform Institutional Providers Form (HCFA- 1450/UB–92) and Supporting Statute Section 1853(a) (3) of the Balanced budget Act of 1997:

*Form No.:* HCFA–R–224;

*Use:* Section 1853(a) (3) of the Balanced Budget Act (BBA) requires Medicare+Choice organizations, as well as eligible organizations with risk-sharing contracts under section 1876, to submit encounter data. Data regarding inpatient hospital services are required for periods beginning on or after July 1, 1997. These data may be collected starting January 1, 1998. Other data (as the Secretary deems necessary) may be required beginning July 1, 1998.

The BBA also requires the Secretary to implement a risk adjustment methodology that accounts for variation in per capita costs based on health status, This payment method must be implemented no later than January 1, 2000. The encounter data are necessary to implement a risk adjustment methodology..

Hospital data from the period, July 1, 1997—June 30.1998. will serve as the basis for plan-level estimates of risk adjusted payments. These estimates will be provided to plans by March, 1999, Encounter data collected from subsequent time periods will serve as the basis for actual payments to plans for CY 2000 and beyond.

In implementing the requirements of the BBA, hospitals will submit data to the managed care plan for enrollees who have a hospital discharge using the HCFA- 1450 (UB–92), Uniform Institutional Provider Claim Form. Encounter data for hospital discharges occurring on or aft&- July 1, 1997 are required. While submission from the hospital to the plan is required, plans are provided with a start-up period during which time an alternate submission route is permitted.

**§ 10.85 Advisory opinions.**

(a) An interested person may request an advisory opinion from the Commissioner on a matter of general applicability.

(1) The request will be granted whenever feasible.

(2) The request may be denied if:

(i) The request contains incomplete information on which to base an informed advisory opinion;

(ii) The Commissioner concludes that an advisory opinion cannot reasonably be given on the matter involved;

(iii) The matter is adequately covered by a prior advisory opinion or a regulation;

(iv) The request covers a particular product or ingredient or label and does not raise a policy issue of broad applicability; or

(v) The Commissioner otherwise concludes that an advisory opinion would *not* be in *t&e* public interest.

(b) A request for an advisory opinion is to be submitted in accordance with §10.20, is subject to the provisions of §10.30 (c) through (l), and must be in the following form:

(Date) _____

Dockets Management Branch, Food and Drug Administration, Department of Health and Human Services, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

REQUEST FOR ADVISORY OPINION

The undersigned submits this request for an advisory opinion of the co-oner of Food and Drugs with respect to ——— (the general nature of the matter involved).

*A. Issues* involved.

(A concise statement of the issues and questions on which an opinion is requested.)

B. *Statement of facts and law.*

(A full statement of all facts and legal points relevant to the request.)

The undersigned certifies that, to the best of his/her knowledge and belief, this request includes all data, information, and views relevant to the matter, whether favorable or unfavorable to the position of the undersigned, which is the subject of the request.

(Signature) _____
(Person making request) _____
(Mailing address) _____
(Telephone number) _____

(c) The Commissioner may respond to an oral or written request to the agency as a request for an advisory opinion, in which case the request will be filed with the Dockets Management Branch and be subject to this section.

(d) A statement of policy or interpretation made in the following documents, unless subsequently repudiated by the agency or overruled by a court, will constitute an advisory opinion:

(1) Any portion of a FEDERAL REGISTER notice other than the text of a proposed or final regulation, e.g., a notice to manufacturers or a preamble to a proposed or final regulation.

(2) Trade Correspondence (T.C. Nos. 1-431 and 1A-8A) issued by FDA between 1938 and 1946.

(3) Compliance policy guides issued by FDA beginning in 1968 and codified in the Compliance Policy Guides manual.

(4) Other documents specifically identified as advisory opinions, e.g., advisory opinions on the performance standard for diagnostic X-ray systems, issued before July 1, 1975, and filed in a permanent public file for prior advisory opinions maintained by the Freedom of Information Staff (HFI-35).

(5) Guidelines issued by FDA under §10.90(b).

(e) An advisory opinion represents the formal position of FDA on a matter and except as provided in paragraph (f) of this section, obligates the agency to follow it until it is amended or revoked. The Commissioner may not recommend legal action against a person or product with respect to au action taken in conformity with an advisory opinion which has not been amended or revoked.

(f) In unusual situations involving an immediate and significant danger to health, the Commissioner mar take appropriate civil enforcement action contrary to an advisory opinion before amending or revoking the opinion. This action may be taken only with the approval of the Commissioner, who may not delegate this function. Appropriate amendment or revocation of the advisory opinion involved will be expedited.

(g) An advisory opinion may be amended or revoked at any time after it has been issued. Notice of amendment or revocation will be given in the same manner as notice of the advisory opinion was originally given or in the FEDERAL REGISTER, and will be placed on public display as part of the file on

the matter in the office of the Dockets Management Branch. The Dockets Management Branch shall maintain a separate chronological index of all advisory opinions filed. The index will specify the date of the request for the advisory opinion, the date Of the opinion, and identification of the appropriate file.

(h) Action undertaken or completed in conformity with an advisory opinion which has subsequently been amended or revoked is acceptable to FDA unless the Commissioner determines that substantial *public* interest considerations preclude continued acceptance. when.. ever possible, an amended or revoked advisory opinion will state when action previously undertaken or completed does not remain acceptable, and any transition period that may be applicable.

(i) An interested person may submit written comments on an advisory opinion or modified advisory opinion. Four copies of any comments are to be sent to the Dockets Management Branch for inclusion in the public file on the advisory opinion. Individuals may submit only one copy. Comments will be considered in determining whether further modification of an advisory opinion is warranted.

(j) An advisory opinion may be used in administrative or court proceedings to Illustrate acceptable and unacceptable procedures or standards, bat not as a legal requirement.

(k) A statement made or advice provided by an FDA employee constitutes an advisory opinion only if it is issued in writing under this section. A statement or advice given by an FDA employee orally, or given in writing bat not under this section or §10.90, is an informal communication that represents the best judgment of that employee at that time but does not constitute au advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

[44 FR 22323, Apr. 13, 1979, as amended at 46 FR 8455, Jan. 27, 1981; 59 FR 14364, Mar. 28, 1994]

### §10.90 Food and Drug Administration regulations, guidelines, recommendations, and agreements.

(a) *Regulations.* FDA regulations are promulgated in the FEDERAL REGISTER under §10.40 or §10.50 and codified in the Code of Federal Regulations. Regulations may contain provisions that will be enforced as legal requirements, or which are intended only as guidelines and recommendations, or both. The dissemination of draft notices and regulations is subject to §10.80.

(b) *Guidelines.* FDA guidelines are included in the public file of guidelines established by the Dockets Management Branch, under this paragraph, unless they have been published as regulations under paragraph (a) of this section.

(1) Guidelines establish principles or practices of general applicability and do not include decisions or advice on particular situations. Guidelines relate to performance characteristics, preclinical and clinical test procedures, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling, or other technical or policy criteria. Guidelines state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA for a subject matter which falls within the laws administered by the Commissioner.

(i) A person may rely upon a guideline with assurance that it is acceptable to FDA, or may follow different procedures or standards. When different procedures or standards are chosen, a person may, but is not required to, discuss the matter in advance with FDA to prevent the expenditure of money and effort on activity that may later be determined to be unacceptable.

(ii) Use of testing guidelines established by FDA assures acceptance of a test a5 scientifically valid, if properly conducted, but does not assure approval of any ingredient or product so tested. Test results or other available information may require disapproval or additional testing.

(2) A guideline represents the formal position of FDA on a matter and, except as provided in paragraph (b)(3) of this section, obligates the agency to