International Academy
of Compounding Pharmacists

P.O. Box 1365
Sugar Land, Texas 77487

281/933-8400 voice
281/495-0602 fax
1-800-927-4227

http://www.compassnet.com/~iacp/.

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

Re: Docket Number 98N-0182
Bulk Drug Substances To Be Used In Pharmacy Compounding: Request For Nominations

Dear Sir or Madam:

The following comments are submitted by the International Academy of Compounding Pharmacists (IACP) in response to the Food and Drug Administration's (FDA's) request for nominations of bulk drug substances that may be used in pharmacy compounding. 63 Fed. Reg. 17011 (April 7, 1998). IACP believes that the amount of information requested by FDA for each nominated substance is excessive and beyond the authority granted to the agency in accordance with Section 503A of the Food, Drug, and Cosmetic Act (FDC Act). Moreover, FDA is calling for the submission of information that is contrary to the very nature of pharmacy compounding. IACP also has several other concerns, described below. IACP requests that FDA publish a notice in the Federal Register to resolve these issues.

As a preliminary matter, we are concerned that FDA declined to commit that it would review all submissions. Our concern is

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heightened by FDA's failure to say when it will review the drugs it does not review initially. In view of the November 21 effective date for Section 503A, we believe FDA should commit to review in a timely manner all drugs that are submitted.

FDA should also promptly publish its proposed criteria for the selection of bulk drug substances in the *Federal Register*. Section 503A specifically directs FDA to develop "criteria" for the selection of bulk drug substances, including consideration of the historical use of the drug substance, reports from peer reviewed medical journals and "other criteria as the Secretary may identify." § 503A(d)(2). However, FDA's notice and request for nominations fails to articulate any specific criteria for the selection and approval of bulk drug substances. Rather, the agency identifies only the types of information to be provided on each nominated substance; it provides no guidance on the factors that will be critical to the approval process. A list of informational categories is not the same as criteria.

The lack of clearly defined selection criteria to guide the content of submissions can only result in great variability in those submissions. This increases the potential that the selection process will be prone to arbitrary, or at least, inconsistent decision making. Furthermore, FDA has indicated that nominations supported by "the most complete and relevant information will likely be evaluated first"; increasing the

likelihood that those substances will appear on the first published list. 63 Fed. Reg. at 17012. However, without more specific criteria, it will be impossible for petitioners to determine what information is most "relevant." In addition, the notice provides that if the requested information is unknown or unavailable, that fact should be noted. However, IACP has been advised that FDA officials have stated that the agency intends to reject – outright – any nomination that does not include all of the information requested. This interpretation would be inconsistent with § 503A(d)(2) and should be expressly repudiated by FDA. To ensure fairness and transparency in the review process, FDA must state the criteria that it will use in evaluating petitions.

Although the notice fails to identify FDA's proposed selection criteria, the nature and extent of the information requested strongly suggests that FDA intends to evaluate compounded drugs by the standards similar to those applicable to new drug applications (NDAs). FDA requests a bibliography of available safety and efficacy data on each nominated drug substance. While an explanatory footnote advises that the lack of safety and efficacy data comparable to that required for an NDA would not "preclude" a bulk drug substance from consideration, it is likely that the availability of such data will weigh very heavily in FDA's evaluation. FDA's intent to apply these standards was reflected in a January 29, 1998

communication from FDA to the state boards of pharmacy (copy enclosed). This included a copy of a message from FDA's Home Page indicating that FDA would request safety and effectiveness data on bulk drug substances. By referring only to safety and effectiveness data, the message demonstrated that FDA would give disproportionate weight to these two elements.

FDA's requests for data relating to safety and effectiveness ignore that Congress specifically exempted compounded drugs from the safety and efficacy standards applied to NDAs. At the same time, Congress imposed other conditions on the practice of compounding to ensure the quality of compounded drugs.[1/] Moreover, the conferees involved in finalizing Section 503A intended that "where evidence relating to an approval under Section 505 does not exist, the Secretary shall consider other criteria."[1/] FDA cannot try to impose NDA-like standards on compounded drugs. IACP specifically requests that FDA clarify that petitions may contain safety and effectiveness data, if available, but such data are not needed for a drug to be listed

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1/ 143 Cong. Rec. S9840 (daily ed. Sep. 24, 1997) (comments of Senator Kennedy).

2/ H.R. CONF. REP. No. 399, 105th Cong., 1st Sess. 95 (1997).

and that safety and efficacy data are simply one of a number of types of information that may be sufficient to secure listing.

In addition, Section 503A provides that compounded drugs must comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding. In the selection of source drugs for compounding that are not subject to a USP or National Formulary monograph, this reference requires the pharmacist to "establish purity and safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source."[1/] Thus, by including this reference in Section 503A it was the intent of Congress that a professional standard apply to the selection of bulk drug substances for compounding. However, FDA's request for data on the safety and purity of nominated substances (as well as data on the strength and quality of the substances) reflects an intent to substitute the agency's judgement for that of the pharmacist. As a result, the ability of a licensed pharmacist or physician to evaluate the appropriateness of a customized compounded substance for an individual patient will be compromised by FDA's applying safety and effectiveness standards designed for mass-produced drugs.

3/ United States Pharmacopoeia, Drug Information Volume III: Approved Drug Products and Legal Requirements, v/102 (18th ed. 1998).

Finally, FDA's request is contrary to the very nature of compounding because it characterizes compounded drugs as "products." This request exerts a level of regulation over the practice of compounding not supported by statute. Section 503A directs FDA to develop criteria for the selection of the bulk drug substances that will be used in compounding; however, FDA was given no authority to develop criteria for approval of the specific drug formulation that result from the compounding process. Thus, FDA's request for any information on compounded drugs is inappropriate.

The essence of compounding is tailoring medication to individual patients. Yet, FDA has requested specific information on the dosage forms into which drugs will be compounded, as well as the intended strengths and routes of administration. This request is at odds with one of the key features of compounding, as it assumes a level of constancy in the formulations prescribed by physicians for compounding. Thus, FDA fails to appreciate that the essential purpose of the practice of compounding is to address the special needs of individual patients, which makes it impossible to identify all of the possible compounded "drug products" that might be prescribed. Asking for information on the varying strengths, dosage forms, routes of administration, or stability of those medications compounded to meet unique patient needs is antithetical to the nature of compounding.

We also believe that it is imperative that FDA provide a written explanation for a decision to deny a petition. This will promote several objectives, such as increasing consistency of decision-making, enhancing the transparency of the process, and providing guidance for future petitions and amendments to rejected petitions.

FDA's failure to provide adequate information by which to develop responsive submissions for nominated bulk drug substances jeopardizes the availability of potentially critical drug substances. Moreover, FDA's attempt to incorporate traditional safety and effectiveness criteria from the process for approving drug products to the practice of pharmacy compounding directly contradicts the intent of Congress in passing Section 503A, and further compromises the care of patients for whom physicians have determined that a compounded drug is medically appropriate.

IACP therefore requests that FDA immediately commit to the prompt review of all petitions, clarify that not all categories of information listed in the Federal Register are required, clearly state that safety and efficacy data are not essential for approval and explain how other data will suffice, identify the criteria for listing drugs, and commit to providing a clear written rationale for any decision denying a petition.

The International Academy of Compounding Pharmacists is a nationally recognized, professional, non-profit, association of 1200 compounding pharmacists in the United States, Canada, Spain, and Chile. IACP seeks to increase awareness of the importance of pharmaceutical compounding and encourage high standards throughout the profession of pharmacy.

Sincerely,

Gina Ford, R.Ph.
Executive Director
International Academy of
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Re: Dockets Number 98N-0182
Bulk Drug Substances To Be Used In Pharmacy Compounding:
Request For Nominations

Dear Sir or Madame:

As per Section 127 of the Food and Drug Administration Modernization Act of 1997 the International Academy of Compounding Pharmacists is nominating 24 bulk drug substances as candidates for the bulk drug list. These substances do not comply with the standards of an applicable USP or NF monograph nor are they components of drugs approved by the FDA, therefore supporting data is being provided to meet criteria set forth by FDA for inclusion on the list of bulk drug substances that may be used in compounding. Each nomination is contained in an individual folder including ingredient, chemical, and common names. Chemical grade or description and information on how the ingredient is supplied is so annotated. Also, information about recognition in foreign pharmacopeias and bibliographies of available safety and efficacy data is included. Requirements such as information on dosage forms, strength, and route of administration have been addressed along with stability data, any formulations or other miscellaneous information.

To support this data as requested by FDA, numerous documents and references have been included in each folder. For example, the melting point maybe found on a quality control report or the description of a substance is contained on a certificate of analysis. Material Safety Data Sheets are included in every folder, which provide health

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hazard or toxicity data, reactivity data as well as handling precautions. Also, included are monographs from *Martindale's Pharmacopeia* and *The Merck Index*. Where applicable each folder contains current abstracts and articles that further support doses, dosage forms, therapy guidelines and cross-over trials with results.

In accordance with the bulk drug provisions in section 127, IACP requested that the United States Pharmacopeial Convention, Inc. and an advisory committee on compounding evaluate these 24 substances. Upon completion of this review process, IACP requests that these substances appear on the list of bulk drug substances that may be used in compounding.

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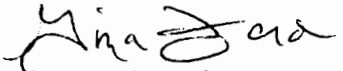

Gina Ford, R.Ph.
Executive Director
International Academy of Compounding Pharmacists