

Memorandum

To: Board Members

Date: January 16, 2008

From: Board of Pharmacy

Subject: Regulation Hearing – Proposal to Repeal 16 CCR § 1716.1 and 1716.2, and Amend §§ 1751-1751.8, and Adopt §§ 1735-1735.8

At this meeting the board will be conducting a regulation hearing to hear testimony about the regulation proposal that establishes requirements for pharmacies that compound medications.

Currently pharmacy law provides the authority for a pharmacist to compound drug products as well as compound sterile injectable products. As required in Business and Professions Code section 4127 the board adopted regulations to implement the provisions for pharmacies that compound sterile injectable products. There are no similar provisions in regulation to detail the requirements for pharmacies that complete general compounding.

In 2004 the Board of Pharmacy formed a Work Group on Compounding comprised of board members, board staff and industry representatives. The workgroup recognized that current pharmacy regulations addressing compounding only govern the physical circumstances, procedures and record keeping requirements for general compounding and do not address quality, strength or purity. At the conclusion of this workgroup, recommendations to change the current regulations were provided.

The board has continued to refine the language based on subsequent comments from interest parties during board and committee meeting as well as included changes recommended by counsel.

At the October 2007 Board Meeting, the board voted to approve the language as presented and initiate the 45-day comment period as required by the Administrative Procedures Act. This regulation was noticed on November 16, 2007. The 45-day comment period was scheduled to end on December 31, 2007, however the board received a request for a hearing on the matter. This request extended the comment period through the regulation hearing.

To date, the board has received a total of seven comments, six from industry and one from counsel. For your review, copies of the comments submitted and board staff responses to comments from industry are provided in **ATTACHMENT A**. Comments received by Dan Wills were submitted on January 15, 2007. Board responses to these comments will be provided at the board meeting.

During the regulation hearing additional testimony will be provided for board consideration. At the conclusion of the hearing the board may consider revising the language. Any changes to the language will result in either an additional 15-day comment period or a new 45-day comment period depending on the scope of the changes.

Attachment A

Comments Received From:

- Victoria Ferrarest, PharmD, and Barbara Burgess, RN, Pathways Home Health & Hospice
- Dawn Benton, Interim Executive Vice President, California Society of Health-Systems Pharmacists
- Michael M. Levy, Jr. Director, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research, Food and Drug Administration
- Joe Grasela
- William J. Blair, PharmD, Director of Pharmacy Services, McGuff Compounding Pharmacy Services, Inc.
- Dan Wills, MBA, Manager, Grandpa's Compounding Pharmacy

Board Response to Comments and Comments from Counsel



PATHWAYS

Home Health & Hospice

RECEIVED BY CALIF.
BOARD OF PHARMACY

2007 DEC 24 PM 4:40

Anne Sodergren
California Board of Pharmacy
1625 N. Market Blvd, Suite N219
Sacramento, CA 95834

December 21, 2007

Dear Ms Sodergren:

We would like to comment on the draft regulations regarding pharmacy compounding www.pharmacy.ca.gov/laws_regs/1716_exact.pdf on behalf of Pathways Home Health & Hospice.

In the proposed regulation, the Board of Pharmacy defines what compounding is, and what it is not.

We are requesting that you add an additional item to the definition of what compounding is not:

"Placement of a patient's legally prescribed medication from the labeled pharmacy container into an oral dosing syringe or a medication organizer to assist the patient in self-administration."

One of the responsibilities of nurses in the home health setting is to assist patients with the management of their medications. This generally includes assuring that patients make safe use of medications through education and enhanced compliance. Nurses frequently pre-fill medication organizers (e.g. Medisets) and draw liquid medications into oral dosing syringes to accomplish this.

The California Nurse Practice Act specifically allows a nurse to place a patient's legally prescribed medication from the labeled pharmacy container into a medication organizer to assist the patient in self-administration.

(See the frequently asked questions concerning a nurses' scope of practice at www.n.ca.gov/pdfs/regulations/npr-b-44.pdf)

In our opinion, drawing liquid medications into oral dosing syringes to facilitate compliance is equivalent to filling a medication organizer with tablets or capsules. An opinion from the Department of Social Services pertaining to residents of Residential Care Facilities for the Elderly (RCFEs) maintains that this is "compounding". (See e-mail communication that follows.)

We strongly disagree; we assert that this is not compounding, and hope that you will consider adding this point to the compounding regulation so that home health and hospice nurses can continue to assist patients with safe medication use wherever they live.

Sincerely,

Victoria Ferraresi

Victoria Ferraresi, PharmD
Director of Pharmacy Services

Barbara Burgess, CEO

Barbara Burgess, RN
Chief Executive Officer

From: Harris, Margie@DSS [mailto:Margie.Harris@dss.ca.gov]
Sent: Tuesday, November 27, 2007 8:39 AM
To: Linda Conti
Subject: Hospice Care in an RCFE

Hi Linda,

I have received an answer to your question concerning pre-filling the oral syringes with morphine for later use at the facility. The policy analyst contacted the Department's pharmacy consultant who responded with the following statement: **"A nurse may prepare an oral syringe of morphine solution at dosing time and administer the medication. However, when preparing multiple oral syringes of morphine sulfate solution, the nurse is performing the function of compounding, which is the relegated role of a pharmacist."** The policy analyst has sent several questions involving pain management of hospice residents in an RCFE to the legal department. Unfortunately most of the caregivers providing care and supervision in the facilities do not possess the medical license that allows them to administer pain medication, which is the major issue facing the resident's end of life care. I will continue to keep you informed. Sorry this process takes so long.

Margie Harris
Licensing Program Analyst
Department of Social Services
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"Philip Swanger"
<philip@cshp.org>
12/20/2007 05:00 PM

To <anne_sodergren@dca.ca.gov>
cc "Dawn Benton" <dbenton@cshp.org>, "Bryce W. A. Docherty" <bryce@thedochertygroup.com>
bcc
Subject Proposed Compounding Regulations



December 20, 2007

Virginia Herold
Executive Officer
California Board of Pharmacy
1625 N. Market Blvd N219
Sacramento, California 95834
Virginia_Herold@dca.ca.gov

Re: Proposed Regulations - Article 4.5 Compounding and Article 7 Sterile Injectable Compounding

Dear Executive Officer Herold:

The California Society of Health-System Pharmacists (CSHP) commends and supports the Board of Pharmacy for their efforts in strengthening the regulations surrounding compounding. However, CSHP expresses concern that the proposed language of Article 4.5 "Compounding" language which also pertains to Article 7 "Sterile Injectable Compounding" will negatively impact the preparation of one-time, short duration, and immediate-need injectable products. More specifically, CSHP is concerned that the added documentation requirements will delay the preparation and delivery of these urgently needed medications in acute care facilities without any additional benefits to patient safety and care.

It is common practice for a pharmacy in an acute care facility to prepare emergency medications for the treatment of MI, stroke, and other life-threatening situations. Currently, these medications are prepared in the pharmacy and labeled with adequate information to assure patient safety and recall should such a medication be recalled in the next few hours during the administration of the medication. Additional record keeping or generation of a pharmacy specific lot number for each IV syringe, Piggyback or Large Volume Parenteral compounded does not serve the patient. It only delays medication preparation and delivery to the patient and places an additional burden on the pharmacy.

In the interest of patient safety, CSHP recommends the following amendment clarifying immediate need sterile injectable products in acute care facilities.

Section 1751.1 Sterile Injectable Recordkeeping Requirements

(a) Pharmacies compounding sterile injectable products for future use pursuant to section 1735.2 shall, in addition to those records required by section 1735.3, make and keep records indicating the name, lot number, amount, and date on which the products were provided to a prescriber.

(b) Pharmacies in an acute care facility compounding sterile injectable products for the immediate needs of a patient may record required components of section 1735.3 on the patient-specific product label instead of records maintained in the pharmacy unless otherwise specified below.

1. Immediate need is defined as medication administration is completed within 24 hours.
2. Master formula record including equipment used in compounding the drug must be readily retrievable in the pharmacy.
3. Manufacturer or supplier and lot number of each component must be readily retrievable in the pharmacy.
4. Pharmacy assigned reference or lot number for the compounded drug is not required.

~~(bc)~~ In addition to the records required by section 1735.3 and subdivision (a), for sterile products compound from one or more non-sterile ingredients, the following records must be made and kept by the pharmacy:

1. The training and competency evaluation of employees in sterile product procedures.
2. Refrigerator and freezer temperatures.
3. Certification of the sterile compound environment.
4. Other facility quality control logs specific to the pharmacy's policies and procedures (e.g. cleaning logs for the facilities and equipment).
5. Inspection for expired or recalled pharmaceutical products or raw ingredients.
6. Preparation records including the master work sheet, the preparation work sheet and records of end-product evaluation results.

~~(ed)~~ Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date of the record was created.

In addition for clarity we suggest the following addition to:

Section 1735.3 Records of Compound Drug Products

(a) Except as specified in Section 1751.1, for each compounded drug product, the pharmacy records shall include:

1. The master formula record
2. The date the drug was compounded.

3. The identity of the pharmacy personnel who compounded the drug product.
4. The identity of the pharmacist reviewing the final drug product.
5. The quantity of each component used in compound the drug product.
6. The manufacturer or supplier and lot number or each component.
7. The equipment used in compounding the drug product.
8. A pharmacy assigned reference or lot number for the compounded drug product.
9. The expiration date of the final compounded drug product.
10. The quantity or amount of drug product compounded.

Founded in 1962, CSHP is a professional society representing more than 4,000 pharmacists and associates who serve patients and the public by promoting wellness and the best use of medications. CSHP members practice in a variety of organized health care settings including, but not limited to hospitals, integrated healthcare systems, clinics, home health care and ambulatory settings.

If you have any questions, please do not hesitate to contact me at (916) 447-1033 or CSHP's Legislative Advocate, Bryce Docherty at (916) 446-4343.

Respectfully,



Dawn Benton
Interim, Executive Vice President

cc. Bryce Docherty



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Virginia Herold
Executive Officer
California State Board of Pharmacy
1625 North Market Blvd., Suite N219
Sacramento, California 95834

Dear Ms. Herold:

Thank you for giving us the opportunity to comment on proposed regulations of the California State Board of Pharmacy that relate to compounding, including requirements for nonsterile and sterile compounding.¹

A. Background

We have prepared an appendix that generally explains FDA's regulatory approach to compounding and the historic and legal background of this approach. *See* Appendix A. In short, FDA's position is that compounded drugs are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act ("the Act" or "FDCA") that, like all such drugs, are subject to the Act's pre-approval requirement. Although virtually all compounded drugs fail to meet this legal requirement, FDA has long recognized the important public health function served by traditional compounding, wherein a pharmacist extemporaneously combines, mixes, or alters drug ingredients in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. Accordingly, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, and misbranding provisions of the Act.

FDA's current enforcement policy with respect to compounding of human drugs is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA's Center for Drug Evaluation and Research on May 29, 2002 (*see Notice of Availability*, 67 *Fed. Reg.* 39,409 (June 7, 2002)). The CPG lists factors that the agency considers in deciding whether and how to exercise its enforcement discretion with respect to compounding. *See* Appendix B. As discussed more specifically below, some provisions of the proposed regulations implicate factors in the CPG.

¹Our comments pertain to §§ 1735-1735.8 and §§ 1751-1751.8 of Division 17 of Title 16 of the California Code of Regulations and focus on the proposed regulations addressing the compounding of human drugs.

FDA is concerned about the public health threat posed by inappropriate drug compounding. This activity has resulted in patient harm and death, and undermines the integrity of the FDCA and the public health protection that it provides. Appendix C discusses examples of some of the concerns and enforcement actions taken by FDA regarding compounded drugs.

While FDA supports some of the provisions of the proposed regulations as appropriate limitations on compounding, FDA is concerned that some of the proposed regulations would purport to legalize conduct that runs afoul of the factors in our current CPG and would be inconsistent with FDA's enforcement policy for compounded drugs. This concerns us because the proposed regulations would not provide a safe harbor against federal enforcement.

B. Compounding Copies of FDA-Approved Drugs

As discussed above and as referenced in Appendices A and B, FDA believes that traditional compounding occurs when a pharmacist extemporaneously combines, mixes, or alters drug ingredients in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient.

The proposed definition of "compounding" in § 1735(c) states that:

Compounding' does not include, except in small quantities under limited circumstances as justified by a specific, documented, medical need, preparation of a compounded drug product that is commercially available in the marketplace or that is essentially a copy of a drug product that is commercially available in the marketplace.

FDA's CPG identifies compounding copies of commercially available, FDA-approved drugs as a factor that FDA considers in determining whether to take enforcement action. The CPG states that the Agency intends to assess whether a pharmacy engages in, among other things:

Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.

The proposed regulation appears to permit compounding of commercially available drug products in small quantities based on a documented medical need. FDA suggests that the language "that is commercially available in the marketplace or" be struck.

Compounding copies of commercially available, FDA-approved drugs is not permitted by the FDCA and is at odds with FDA's enforcement policy under the CPG. Further, FDA believes that pharmacists should compound near copies of commercially available, FDA-approved drugs only when the drug is needed to produce for a patient a significant medical difference that is not afforded by a commercially available, FDA-approved drug product. Absent this medical need, such compounding is inappropriate even when it occurs in small quantities.

C. Comments on Proposed Compounding Definition

Proposed § 1735.1(c) states that "quality" means the absence of harmful contaminants, including filth, putrid, or decomposed substances, and absence of active ingredients other than those noted on the label." FDA suggests that the definition also include other elements of quality mentioned in the FDCA, such as the requirement that a drug representing itself as a drug the name of which is recognized in an official compendium must meet the compendial standards. 21 U.S.C. §351(b). For non-compendial drugs, the drug should meet the quality standards it purports to possess. 21 U.S.C. § 351(c).

D. Compounding Limitations and Requirements

1. Compounding Drugs for Prescribers

The proposed regulation at § 1735.2(c) states that

'a reasonable quantity' of compounded drug product may be furnished to a prescriber for office use upon prescriber order, where "reasonable quantity" is that amount of compounded drug product that

- (1) is sufficient for administration or application to patients in the prescriber's office or for distribution of not more than a 72-hour supply to the prescriber's patients as estimated by the prescriber; and
- (2) is reasonable considering the intended use of the compounded medication and the nature of the prescriber's practice; and
- (3) for any individual prescriber and for all prescribers taken as a whole, is an amount which the pharmacy is capable of compounding in compliance with pharmaceutical standards for integrity, potency, quality and strength of the compounded drug product.

FDA is concerned that the proposed regulation may permit activities that go beyond traditional pharmacy compounding and would implicate several factors in the CPG, including:

- whether a firm compounds drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;

-
- whether a firm compounds drugs for third parties who resell them to individual patients or offers compounded drugs at wholesale to other state licensed persons or commercial entities for resale; and
 - whether a firm compounds large quantities of standardized drugs.

FDA recognizes that it may be appropriate in some circumstances for pharmacists to compound minimal quantities of drugs solely for administration in a practitioner's office when commercially available, FDA-approved drugs cannot meet the medical needs of specific patients of the practitioner. However, FDA is concerned that the proposed regulation does not include sufficient limitations and safeguards and therefore is potentially inconsistent with FDA's enforcement policy regarding compounded drugs. For instance, it is unclear what "pharmaceutical standards" would apply to the amount of compounded drug product to be furnished to a prescriber. FDA proposes that the specific pharmaceutical standards for integrity, purity, quality and strength be articulated in the regulations. FDA also suggests that the regulations provide that the pharmacy maintain documentation identifying the patients to whom the compounded drug was administered. Methods for identification could include a practitioner's agreement to identify to the pharmacy the patients who received the compounded drug.

In addition, FDA believes that the proposed regulation could be strengthened with respect to the provision of compounded drugs to practitioners by prohibiting the pharmacy or pharmacist from compounding drugs for practitioners that will be sold by the practitioners to other persons or entities (other than the patient being administered the drug). Further, FDA believes the proposed regulation could be strengthened by requiring that labels of drugs compounded for practitioners who will be administering the drug to patients be labeled with the statement "For Office Use Only – Not for Resale."

We also point out that distribution of prescription drugs to a practitioner may constitute the wholesale distribution of drugs under the FDCA (as amended by the Prescription Drug Marketing Act) and its implementing regulations. "Wholesale distribution" is defined as "the distribution of prescription drugs to persons other than a consumer or patient, but excludes the "sale, purchase, or trade of a drug, an offer to sell, purchase, or trade a drug, or the dispensing of a drug pursuant to a prescription" and excludes "[t]he sale of minimal quantities of drugs by retail pharmacies to licensed practitioners for office use." 21 C.F.R. §§ 205.3(f)(6) and (10). Wholesale distributors of prescription drugs must be licensed by a state in accordance with certain requirements. *See* 21 U.S.C. § 353(e)(2)(B) and 21 C.F.R. Part 205. In particular, 21 C.F.R. § 205.4 requires wholesale distributors to be licensed by the state licensing authority in accordance with Part 205 before engaging in the interstate wholesale distribution of prescription drugs.

2. Beyond-Use Date

Proposed § 1735.2(h) requires that compounded drug products be given an expiration or beyond use date. According to this section:

this 'beyond use date' of the compounded drug products shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging.

We believe that a general beyond use date of no more than 180 days for compounded drug products may not be supported by data or by recognized references. For example, USP's Chapter 795 provides specific beyond use date requirements for certain classes of compounded products, including: (1) non-aqueous liquids and solid formulations; (2) water-containing formulations; and (3) all other formulations. The compendial beyond use dates appear to reflect the type of formulation and therefore may provide a more appropriate beyond use date.

Furthermore, it is unclear whether this maximum beyond use date of 180 days would apply to sterile compounded products. If it does, the beyond use date seems excessive since sterility may not be assured without preservatives or other conditions that are not captured in the regulations. Last, FDA suggests that the "stability studies" to support a beyond use date described in § 1735.2(h) be those studies be from a known, reliable source so that such data are valid.

3. Self Assessment Form for Compounding Pharmacies

Proposed section 1735.2(j) describes the annual completion by the pharmacist-in-charge of a self-assessment form for compounding pharmacies. It is our understanding that this form will not replace an inspection, but instead will be reviewed at inspection, along with pharmacy practices, procedures and records to determine whether the pharmacy complies with the applicable provisions on pharmacy compounding. The agency agrees that the form cannot take the place of the required procedures and recordkeeping requirements nor of an inspection to determine compliance.

E. Sterile Injectable Compounding

With respect to the proposed regulations on "Sterile Injectable Compounding," FDA notes that there are no provisions for other types of sterile preparations, such as ophthalmic preparations. Such preparations are required to be sterile, and pharmacies that prepare such preparations and other sterile preparations should follow appropriate practices to ensure product sterility.²

F. Technical Amendments

The agency also has technical comments on the proposed regulation. We offer them in the text below.

² See 21 C.F.R. § 200.50. See Appendix D, providing our comments to USP on Chapter 797 and reflecting our concerns about sterile pharmacy compounding.

FDA suggests that the written master formula record described in § 1735.2(d) be amended to include 2 additional items: the source of the active pharmaceutical ingredient and the lot number.

Proposed § 1735.3(c) states that chemicals, bulk drug substances, drug products, and components for compounding be obtained from reliable suppliers. Consistent with the policy articulated in our CPG, FDA suggests that such reliable suppliers provide written assurance that each lot of drug substance has been made in an FDA-registered facility.

Section 1735.5(c) describing the compounding policy and procedure manual should include procedures for maintaining records and investigating complaints.

Section 1735.6 describing “compounding facilities and equipment” should include a provision on the methods of cleaning and disinfecting equipment and facilities prior to and after compounding.

Section 1751.1(b) should require a file on complaints.

Section 1751.4(d) requires that surfaces in designated areas be disinfected weekly. The agency is concerned that disinfecting these areas weekly may be insufficient, and we refer you to our comments to the United States Pharmacopeia on its Chapter 797.

Section 1751.5(a) states that gowns and gloves shall be worn when preparing cytotoxic agents. FDA suggests that such attire should be worn when compounding other sterile drugs.

Proposed § 1751.5(b) states that “[w]hen compounding sterile products from one or more non-sterile ingredients the following standards must be met . . .” FDA suggests striking the phrase “from one or more non-sterile ingredients” since the standards should also apply when compounding sterile products using sterile ingredients. In addition, § 1751.5(b)(3) states that when compounding, sterile gloves should be worn when jewelry cannot be removed. FDA suggests that sterile gloves should always be worn when compounding sterile preparations.

FDA is uncertain why proposed § 1751.5(c) states that the provisions of § 1751.5(b) do not apply if a barrier isolator is used to compound sterile injectable products. Some of the requirements in § 1751.5(b)—such as the removal of jewelry—may in fact apply when a barrier isolator is used. FDA suggests the revision of § 1751.5(c) to clarify which provisions of § 1751.5(b) would apply.

FDA suggests that proposed § 1751.7(a)(3) be revised to add “or complaint” at the end of the sentence, so that the sentence would read:

(3) Actions to be taken in the event of a drug recall or complaint.

Last, FDA suggests that § 1751.7(b) be amended to add “compounding” before the term “technique” that appears in the second line of this section. If this amendment is accepted,

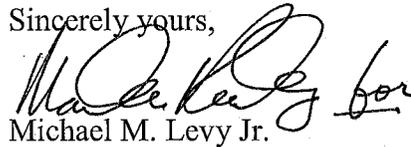
the first sentence of § 1751.7(b) would read: "Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on compounding technique before being allowed to prepare sterile injectable products."

G. Conclusion

Thank you for the opportunity to present FDA's views on the proposed regulations addressing compounding. We hope that our comments and the discussion regarding FDA's regulatory approach to compounded drugs provide assistance to the Board. FDA generally defers to state authorities in the area of traditional pharmacy compounding. However, the agency is prepared to take enforcement action when application of statutory and regulatory factors, as well as the compounding CPG, suggest that enforcement is warranted.

If you have any questions, please feel free to contact us.

Sincerely yours,



Michael M. Levy Jr.

Director

Division of New Drugs and Labeling Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Appendix A ["FDA's Current Enforcement Policy Regarding Compounded Drugs Under the Federal Food, Drug, and Cosmetic Act and FDA's Compliance Policy Guide on Pharmacy Compounding"]

Appendix B [Compliance Policy Guide section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002]

Appendix C [Public Health Concerns and Examples of FDA Enforcement Action Regarding Compounded Drugs]

Appendix D [FDA Comments to United States Pharmacopeia on Proposed Changes to USP Chapter 797, September 22, 2006]

Appendix A

FDA's Current Enforcement Policy Regarding Compounded Drugs Under the Federal Food, Drug, and Cosmetic Act and FDA's Compliance Policy Guide on Pharmacy Compounding.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view is that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"). There is substantial judicial authority supporting FDA's position that compounded drugs are not exempt from the new drug definition. See *Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug . . . provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.¹

The drugs that pharmacists compound are rarely FDA-approved and thus lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced drug, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

¹ In August 2006, the U.S. District Court for the Western District of Texas issued a ruling in *Medical Center Pharmacy v. Gonzales* interpreting, among other things, the application of the "new drug" provisions of the FDCA to compounded drugs. See *Medical Center Pharmacy v. Gonzales*, MO-04-CV-130, (W.D. Tex, Aug. 30, 2006). FDA has filed a notice of appeal to the U.S. Court of Appeals for the Fifth Circuit. The district court's ruling only applies in the Western District of Texas.

FDA's current enforcement policy with respect to the compounding of human drugs is articulated in Compliance Policy Guide section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see *Notice of Availability*, 67 *Fed. Reg.* 39,409 (June 7, 2002)).² The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs and unapproved new animal drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. As stated in the CPG, "[t]he . . . list of factors is not intended to be exhaustive." See CPG section 460.200 ["Pharmacy Compounding"].

The factors identified in the CPG include whether a firm is:

- compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;
- compounding drugs for third parties who resell them to individual patients or offering compounded drugs at wholesale to other state licensed persons or commercial entities for resale;
- compounding drugs that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. However, in certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient;
- compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA sanctioned investigational new drug application (IND);
- receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility; and
- receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.

These are some of the factors that help guide FDA's enforcement decisions and thus describe the kinds of compounding-related conduct that the agency generally regards as most inappropriate.

² Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Ninth Circuit's ruling in *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001), that Section 503A included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

Appendix B

Compliance Policy Guide Compliance Policy Guidance for FDA Staff and Industry¹ CHAPTER - 4 SUB CHAPTER - 460

Sec. 460.200 Pharmacy Compounding

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. 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 statutes and regulations.

INTRODUCTION

This document provides guidance to drug compounders and the staff of the Food and Drug Administration (FDA) on how the Agency intends to address pharmacy compounding of human drugs in the immediate future as a result of the decision of the Supreme Court in Thompson v. Western States Medical Center, No. 01-344, April 29, 2002. FDA is considering the implications of that decision and determining how it intends to regulate pharmacy compounding in the long term. However, FDA recognizes the need for immediate guidance on what types of compounding might be subject to enforcement action under current law. This guidance describes FDA's current thinking on this issue.

BACKGROUND

On March 16, 1992, FDA issued a compliance policy guide (CPG), section 7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. That CPG remained in effect until 1997 when Congress enacted the Food and Drug Administration Modernization Act of 1997.

¹ This guidance has been prepared by the Office of Regulatory Policy and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (the Modernization Act). Section 127 of the Modernization Act added section 503A to the Federal Food, Drug, and Cosmetic Act (the Act), to clarify the status of pharmacy compounding under Federal law. Under section 503A, drug products that were compounded by a pharmacist or physician on a customized basis for an individual patient were entitled to exemptions from three key provisions of the Act: (1) the adulteration provision of section 501(a)(2)(B) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (concerning the approval of drugs under new drug or abbreviated new drug applications). To qualify for these statutory exemptions, a compounded drug product was required to satisfy several requirements, some of which were to be the subject of FDA rulemaking or other actions.

Section 503A of the Act took effect on November 21, 1998, one year after the date of the enactment of the Modernization Act. In November, 1998, the solicitation and advertising provisions of section 503A were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. The U.S. District Court for the District of Nevada ruled in the plaintiffs' favor. FDA appealed to the U.S. Court of Appeals for the Ninth Circuit. On February 6, 2001, the Court of Appeals declared section 503A invalid in its entirety (*Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001)). The government petitioned for a writ of certiorari to the U.S. Supreme Court for review of the circuit court opinion. The Supreme Court granted the writ and issued its decision in the case on April 29, 2002.

The Supreme Court affirmed the 9th Circuit Court of Appeals decision that found section 503A of the Act invalid in its entirety because it contained unconstitutional restrictions on commercial speech (i.e., prohibitions on soliciting prescriptions for and advertising specific compounded drugs). The Court did not rule on, and therefore left in place, the 9th Circuit's holding that the unconstitutional restrictions on commercial speech could not be severed from the rest of section 503A. Accordingly, all of section 503A is now invalid.

FDA has therefore determined that it needs to issue guidance to the compounding industry on what factors the Agency will consider in exercising its enforcement discretion regarding pharmacy compounding.

DISCUSSION

FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.²

² With respect to such activities, 21 U.S.C. 360(g)(1) exempts retail pharmacies from the registration requirements of the Act. The exemption applies to "Pharmacies" that operate in accordance with state law and dispense drugs "upon prescriptions of practitioners licensed to administer such drugs to patients under the care of such practitioners in the

FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities are the focus of this guidance. Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of receiving a valid prescription for them. Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship. Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers.

POLICY:

Generally, FDA will continue to defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. FDA anticipates that, in such cases, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions by the states.

However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action. In determining whether to initiate such an action, the Agency will consider whether the pharmacy engages in any of the following acts:

1. Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.
2. Compounding drugs that were withdrawn or removed from the market for safety reasons. Appendix A provides a list of such drugs that will be updated in the future, as appropriate.

course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail" (emphasis added). See also 21 U.S.C. §§ 374(a)(2) (exempting pharmacies that meet the foregoing criteria from certain inspection provisions) and 353(b)(2) (exempting drugs dispensed by filling a valid prescription from certain misbranding provisions).

3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(f) and 21 CFR 312.
4. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
5. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
6. Using commercial scale manufacturing or testing equipment for compounding drug products.
7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

The foregoing list of factors is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case.

Other FDA guidance interprets or clarifies Agency positions concerning nuclear pharmacy, hospital pharmacy, shared service operations, mail order pharmacy, and the manipulation of approved drug products.

REGULATORY ACTION GUIDANCE:

District offices are encouraged to consult with state regulatory authorities to assure coherent application of this guidance to establishments that are operating outside of the traditional practice of pharmacy.

FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution. Charges may include, but need not be limited to, violations of 21 U.S.C. §§ 351(a)(2)(B), 352(a), 352(f)(1), 352(o), and 355(a) of the Act.

Issued: 3/16/1992
Reissued: 5/29/2002



APPENDIX A

LIST OF COMPOUNDING DRUGS THAT WERE WITHDRAWN OR REMOVED FROM THE MARKET FOR SAFETY REASONS

Adenosine phosphate: All drug products containing adenosine phosphate.
Adrenal cortex: All drug products containing adrenal cortex.
Aminopyrine: All drug products containing aminopyrine.
Astemizole: All drug products containing astemizole.
Azaribine: All drug products containing azaribine.
Benoxaprofen: All drug products containing benoxaprofen.
Bithionol: All drug products containing bithionol.
Bromfenac sodium: All drug products containing bromfenac sodium.
Butamben: All parenteral drug products containing butamben.
Camphorated oil: All drug products containing camphorated oil.
Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.
Casein, iodinated: All drug products containing iodinated casein.
Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.
Chlormadinone acetate: All drug products containing chlormadinone acetate.
Chloroform: All drug products containing chloroform.
Cisapride: All drug products containing cisapride.
Cobalt: All drug products containing cobalt salts (except radioactive forms cobalt and its salts and cobalamin and its derivatives).
Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.
Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.
Dibromsalan: All drug products containing dibromsalan.
Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.
Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.
Dipyron: All drug products containing dipyron.
Encainide hydrochloride: All drug products containing encainide hydrochloride.
Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.
Flosequin: All drug products containing flosequin.
Gelatin: All intravenous drug products containing gelatin.
Glycerol, iodinated: All drug products containing iodinated glycerol.
Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin.
Grepafloxacin: All drug products containing grepafloxacin.
Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate.
Metabromsalan: All drug products containing metabromsalan.
Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.
Methapyrilene: All drug products containing methapyrilene.
Methopholine: All drug products containing methopholine.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.
Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application).
Nomifensine maleate: All drug products containing nomifensine maleate.
Oxyphenisatin: All drug products containing oxyphenisatin.
Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.
Phenacetin: All drug products containing phenacetin.
Phenformin hydrochloride: All drug products containing phenformin hydrochloride.
Pipamazine: All drug products containing pipamazine.
Potassium arsenite: All drug products containing potassium arsenite.
Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).
Povidone: All intravenous drug products containing povidone.
Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.
Sparteine sulfate: All drug products containing sparteine sulfate.
Sulfadimethoxine: All drug products containing sulfadimethoxine.
Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).
Suprofen: All drug products containing suprofen (except ophthalmic solutions).
Sweet spirits of nitre: All drug products containing sweet spirits of nitre.
Temafloracin hydrochloride: All drug products containing temafloracin.
Terfenadine: All drug products containing terfenadine.
3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.
Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.
Ticrynafen: All drug products containing ticrynafen.
Tribromsalan: All drug products containing tribromsalan.
Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.
Troglitazone: All drug products containing troglitazone.
Urethane: All drug products containing urethane.
Vinyl chloride: All aerosol drug products containing vinyl chloride.
Zirconium: All aerosol drug products containing zirconium.
Zomepirac sodium: All drug products containing zomepirac sodium.

Appendix C

The Public Health Concern: Highlights of the Public Health Threat Posed by Inappropriate Compounding and Recent FDA Enforcement Actions in This Area

The public health threat posed by inappropriate drug compounding is the object of FDA concern and enforcement. Improper compounding has caused patient harm and death, and it undermines the federal drug approval process and the public health protection that it provides. The following examples illustrate some of these concerns and enforcement action taken by FDA:

1. In December 2006, FDA warned five firms that compounded high doses of topical anesthetic creams and marketed them for general distribution to laser-hair removal clinics rather than for the unique medical needs of individual patients. Two deaths were connected to the topical anesthetics compounded by two of the pharmacies. FDA-approved topical anesthetic products are commercially available, properly labeled, and regularly used in health care settings. However, these pharmacies created their own versions of these approved products, often including combinations of ingredients and ingredients at higher strengths than found in FDA-approved drugs.
2. In August 2006, FDA warned three firms to stop manufacturing and distributing thousands of doses of unapproved inhalation drugs under the guise of compounding. Warning letters to these firms identify a range of serious concerns posed by their practices, including inadequate quality control, concerns about potency, and compounding what essentially are copies of FDA-approved, commercially-available drugs without any patient-specific need. Inhalation drugs are used to treat potentially life-threatening diseases, including asthma, emphysema, bronchitis, and cystic fibrosis, for which numerous FDA-approved drugs are available.
3. In March 2006, FDA issued a warning letter to a Maryland firm regarding its compounding of cardioplegia solutions – used in open-heart surgery – that were contaminated. The contaminated cardioplegia solutions caused severe systemic infections in five patients at a hospital in Virginia. Three of the five patients died from their infections. FDA laboratories confirmed the presence of several species of bacteria in unopened samples of cardioplegia solution collected from the hospital where the surgeries took place. Following notification by the CDC of the infections, FDA gave public notice of the firm's recall of all injectable products produced by the firm's Maryland facility. The cardioplegia solutions had been distributed to hospitals in 4 states.
4. In August 2005, FDA gave public notice of a nationwide recall concerning a compounded product, Trypan Blue Ophthalmic Solution, that was contaminated with *Pseudomonas aeruginosa* bacteria. The compounded product – which is used in cataract surgery – was distributed to hospitals and clinics in 8 states. Two patients at a Washington, DC, VA Hospital became blind, and the eyesight of several others was damaged after use of the contaminated compounded product.

5. In March 2005, FDA issued a nationwide alert concerning a contaminated compounded magnesium sulfate solution that resulted in five cases of *Serratia marcescens* bacterial infections in patients in a New Jersey hospital. A South Dakota patient treated with the product developed sepsis and died. The product had been distributed to hospitals around the country.
6. In June 2004, FDA issued letters to 6 pharmacies and suppliers regarding the compounding of domperidone for human use, in particular by lactating women to increase breast milk production. FDA also issued a talk paper warning women against using the product. Domperidone is not an active ingredient contained in *any* FDA-approved drug product. There are several published reports and case studies of cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone later withdrawn from marketing in several countries.
7. In September 2002, a compounding pharmacy in South Carolina recalled all lots of its methylprednisolone acetate injectable products based on reports of four patients who developed a rare fungal infection after taking the drug. The compounding pharmacy provided the compounded products to clinics and physicians in multiple states as "office stock." Ultimately, six patients were infected, and one died. A joint FDA/South Carolina Board of Pharmacy inspection revealed that the firm lacked adequate controls over its compounding operation to ensure the necessary sterility. When the firm refused to voluntarily recall other injectable products or to provide FDA with a complete list of all products distributed, FDA issued a nationwide alert on all injectable drugs prepared by the firm.
8. In August 2002, during a joint FDA/New Hampshire Board of Pharmacy inspection, FDA determined that a pharmacy was compounding Fentanyl "lollipops" and dispensing them to patients without the labeling and other packaging and safety features required by FDA for the approved product. Fentanyl is a potent opioid used in anesthesia and intensive care. FDA has approved a lollipop-like lozenge form of Fentanyl, but marketing of the drug is conditioned on specific labeling, packaging, and other restrictions to ensure that the drug is used only when clinically indicated. The compounded "lollipop" was essentially an unapproved copy of the approved, commercially available product, without the required precautionary features. One of the compounded lollipops was confiscated from a high school student, who had taken it from his home. A warning letter was issued to the compounding pharmacy.
9. In September 2002, FDA issued a warning letter to a California pharmacy after it determined during a joint FDA/California inspection that the firm was operating as a drug manufacturer, not as a retail pharmacy. The firm used commercial scale manufacturing equipment, and compounded large quantities of inhalation solution drugs for shipment across California and to other states without prescription orders for individually identified patients. In March 2002, the firm issued a recall of compounded inhalation products due to microbial contamination and the FDA/California inspection concluded that the firm lacked sufficient controls and procedures to comply with good drug manufacturing regulations.

10. In June 2001, a California pharmacy compounded betamethasone injection that was administered by spinal injection to 38 patients and that resulted in eight patients developing meningitis (including three deaths and five hospitalizations). Eight other patients were hospitalized and 22 patients received follow-up medical care. Drug sample analyses reportedly disclosed that the drug product was contaminated with *Serratia marcescens*.

SIF



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 22 2006

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial
Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 9-06-004-O

Dear Ms. Long:

This letter is in regard to the In-Process Revision proposal for General Information Chapter <797> **Pharmaceutical Compounding – Sterile Preparations** that appeared in the May-June 2006 issue of Pharmacopeial Forum (PF), Vol. 32, No. 3, on pages 852-898. We have summarized our general comments, below. Also please find enclosed an edited version of the General Chapter proposal, with our minor editorial comments and corrections highlighted and enumerated in a page-by-page arrangement, for your convenience.

We have also included in this letter our comments on the recent companion USP publication *USP <797> Guidebook to Proposed Revisions*, specifically addressing the section entitled "Enforceability and Recognition of General Chapter <797>."

**Topic I. General Comments on Revised General Chapter <797>
Pharmaceutical Compounding – Sterile Preparations:**

1. Improving Scientific Accuracy

We have found what appear to be scientific inaccuracies in the following topic areas addressed in the chapter: (A) steam sterilization in a pharmacy setting; (B) risk levels for the compounded sterile preparations (CSP); (C) disinfection with isopropanol; (D) environmental monitoring frequency; (E) recommendations on media fills; and (F) storage conditions for CSPs. Some of the requirements are not adequately explained and the recommendations appear to lack a firm scientific basis. Our specific concerns are given below. Please note that the referenced line numbers, included for convenience of reference, refer to the enclosed edited version of the General Chapter:

A. Lack of clarity regarding steam sterilization in a pharmacy setting

1. **Line 668 – Sterilization Methods:** We recommend clearer guidance on steam sterilization or the validation of an autoclave cycle. The lack of guidance may cause confusion and risk producing a non-sterile product. Specifically, it is problematic to state:

“The selected sterilization process is expected from experience and appropriate information sources (e.g., see Sterilization and Sterility Assurance of Compendial Articles <1211>) - and, preferably, verified whenever possible – to achieve sterility in the particular CSPs.”
(Line numbers: 672-675)

The use of the phrase “whenever possible” does not provide meaningful guidance to the individual pharmacist trying to determine whether it is important to “verify” an autoclave sterilization process. This provision would not promote or assure uniform good compounding practices for CSPs. We recommend deleting the words “whenever possible” from the text.

2. **Line 641 - Verification of Compounding Accuracy and Sterility:** This section appears to confuse *sterilization validation* with *sterility testing* by stating:

“For example, sterility testing (see Test for Sterility of the Product to Be Examined under Sterility Tests <71>) may be applied to specimens of low and medium-risk CSPs, and standard nonpathogenic bacterial cultures may be added to nondispensable specimens of high-risk CSPs before terminal sterilization for subsequent evaluation by sterility testing.” (Line numbers: 646-650)

The wording in this section is unclear. The section should make recommendations for sterility testing and for validating that sterilization has occurred. The section on “Steam Sterilization” refers to other USP chapters (e.g., *Biological Indicators <1035>*, *Sterilization <1211>*) that were intended for large-scale drug manufacturers. In some cases, these chapters may be too complex to be readily understood in a CSP context. Chapter <797> does not appear to acknowledge that most pharmacists are not familiar with sterilization validation and would need guidance on how to

conduct validation specific to a pharmacy setting (e.g., the use of a smaller autoclave).

We propose that USP revise this section with specific recommendations tailored to a pharmacy setting. Discussion should include how to conduct sterilization validation using biological indicators inoculated into the product and use of temperature-measuring devices. The routine maintenance of the autoclave to ensure its proper functioning should also be discussed.

B. Use of CSP risk levels is inadvisable and should not be used to set storage times

1. **Line 298 – CSP Microbial Contamination Risk Levels:** The designation of CSP microbial contamination risk levels as low, medium, and high is problematic and should be deleted. All three levels pertain to the production of sterile drug products by aseptic processing (single- vs. multiple-entry and transfer) or terminal sterilization/filter sterilization of non-sterile components. The risk category designations are unsound, particularly from a microbiological risk standpoint, and vulnerable to inappropriate usage. Further, there is no discussion of the need to conduct systematic risk assessment for each facility and for each compounded product.

It would be more scientifically sound to recommend that specific procedures be put in place to address and mitigate the contamination risk, based on the type of operation and the type of drug product being processed.

2. **Lines 335, 380, 435 – Linking CSP Risk Levels to Storage Times:** The risk-level categories referenced above are based mainly on the number of manipulations the CSP undergoes during compounding. These risk categories are then used to set acceptable "storage periods" (maximum time from compounding until use) with lower-risk categories being assigned longer storage times. Although fewer manipulations does indicate that a CSP could have a lower likelihood of contamination, the ability of a microbial contaminant to multiply in the CSP and thus cause harm to the patient is unrelated to the number of manipulations performed during compounding. Thus, the threat to the patient is the same for all risk categories (under the proposed risk assessment scheme), so linking the CSP storage time to the

likelihood of a contaminated CSP does not make sense. Lengthening the storage time might make sense only for a CSP that would not support microbial proliferation of any contaminating microorganism (for example, due to a highly-effective preservative system, or the inherent anti-microbial nature of the CSP). Storage limits for low-, medium-, and high-risk products must be based on the actual physical and chemical properties of a drug product. The storage periods should be supported by stability data and/or scientific knowledge.

3. Line 318: **Using Results from Sterility Tests to Justify Storage Periods:** The following statement regarding the assignment of storage times based on "risk-levels" is included in the chapter text (lines 318-320):

"The pre-administration duration and temperature limits specified in the following low-risk, medium-risk, and high-risk level sections apply in the absence of direct sterility testing results that justify different limits of specific CSPs."

This statement seems to suggest that a satisfactory result from a sterility test would justify a longer storage time for a CSP. A passed sterility test for an aseptically-manipulated CSP unit (or units) provides little, if any, assurance that the other CSP units from the same batch are free of microbial contamination. Therefore, a passed sterility test should not be used to extend storage times for a CSP.

4. Line 414 – **High-Risk Level CSPs:** While we agree that aseptic processing and sterile filtration of a formulation derived from non-sterile components can be of risk, the designation of steam-sterilized product as "high risk" is ill-advised. Instead, the focus on the compounding of non-sterile preparations that are steam sterilized should be on the assessment of the microbial quality (i.e., bioburden level, endotoxin level, and microbial-growth-promoting properties) of the non-sterile components used. The subsequent autoclaving step, if done correctly, will provide a greater assurance of sterility than will aseptic-processing of sterile products. For the above reason, the designation of steam-sterilized product as high-risk CSP lacks a meaningful scientific basis.

C. Disinfection with non-sterile isopropanol

Lines 789, 931, 949, 969, etc.: The chapter prescribes the use of non-sterile 70% isopropanol (IPA) for disinfection, but IPA is a low-to-medium efficacy disinfecting agent that lacks sporicidal activity. Accordingly, we recommend removal of all references to IPA. We recommend instead the use of appropriate, sterile disinfectants in the compounding of sterile preparations. It is important that USP strongly emphasize the practical consequences of a poor disinfecting regimen. Use of inadequate disinfectants and procedures has been directly linked with loss of laminar airflow hood control, product non-sterility, and adverse drug events, including septicemia.

D. Discussion of environmental controls and environmental monitoring frequency must be science- and risk-based

1. **Line 817 – Facility Design and Environmental Controls:** Undue emphasis is placed on environmental controls peripheral to the critical sites of aseptic manipulation. A great deal of effort is spent describing cleanrooms and buffer zones, while the focus should be on the critical zone.
2. **Line 1124 – Environmental Monitoring:** The section on Environmental Monitoring specifically requires active air samplers for airborne environmental monitoring, including for sampling areas peripheral to the aseptic manipulation site (BSCs, LAFWs and CAIs). The section also states that the use of settling plates is not acceptable. Overall, the chapter focuses a great deal of attention on mandating very specific facility design and environmental monitoring requirements. While these issues are certainly important for the compounding of sterile preparations, the most critical factor in manual aseptic operations is the aseptic technique of the individual operator. All of the environmental controls in the world will not make up for an operator with poor technique. However, an operator adept at aseptic technique, using properly functioning equipment (BSC, LAFW or CAI) situated in an appropriate environment (clean, low traffic area with reasonable environmental control and disinfected or sterilized equipment) should be able to safely compound sterile preparations.

3. **Line 1193 – Environmental Monitoring - Sampling Frequency:** This section states that, *“Active electronic air sampling that is designed not to interrupt airflow while sampling shall be performed and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.”* (Line numbers: 1193-1196)

Table 3 provides additional requirements for an environmental monitoring sampling schedule. (Line number: 1242). But this schedule does not provide appropriate requirements on the frequency of **personnel** monitoring. Monitoring frequency is every week for low-risk and medium-risk CSPs. Personnel are the most common vector of contamination in the aseptic preparation of a sterile product, and personnel monitoring should be conducted **daily** for any aseptic compounding operation.

Table 3 also needs revised requirements on the frequency of **surface** monitoring. Monitoring frequency is every week for low-risk and medium-risk CSPs, and daily for high-risk CSPs, although the latter are typically terminally sterilized.

Environmental monitoring should be revised to recommend that daily microbial monitoring be conducted whenever aseptic compounding activity occurs.

4. **Line 1141 – Environmental Monitoring - Sampling Plan:** This section states that:

“Selected sampling sites should include multiple locations within each ISO Class 5 (see Table 1) environment and in the ISO Class 7 and 8 (see Table 1) areas.” (Line numbers: 1141-1142).

We suggest that a sentence be added to state that “sampling sites should reflect those areas that pose the greatest environmental risk to product contamination.”

E. Concerns about the accuracy and scientific basis of recommendations on media fills and sterilization times

1. **Line 358 – Low-Risk Level CSPs – Example of a Media-Fill Test Procedure; Line 397 – Medium-Risk Level CSPs – Example of a Media-Fill Test Procedure:** The media fill examples provided for the three risk levels (Low, Medium, and High) do not address the actual compounding production process. The media fill examples given for Low- and Medium-Risk are very detailed, yet do not appear to simulate actual production conditions or address all types of compounding activities. In addition, when a pharmacy prepares many units of admixture (nutritional admixture in IV bags) on a routine basis, a media fill procedure should simulate the actual preparation scheme and conditions in order to assess the capability of producing a sterile product. The media fill procedure for medium-risk products does not address “open” manipulations such as with ampules. We recommend that ampules be addressed.
2. **Line 462 – High-Risk Level CSPs – Example of a Media-Fill Test Procedure CSPs Sterilized by Filtration:** The high-risk CSPs in <797> result from compounding non-sterile components, followed by steam sterilization. The chapter provides an example of media fill for high-risk CSPs. The purpose of this media fill exercise is unclear. We recommend clarifying that media fill is not needed for products that are terminally sterilized. Media fill applies only to those sterile products that are produced by aseptic processing.
3. **Line 451 – High-Risk Level CSPs – Examples of High-Risk Compounding:** The Chapter permits exposure of sterile ingredients to uncontrolled environments for up to one hour (Line numbers: 451-453, 489, and 493). Sterilized materials should not be exposed to conditions that pose an undue risk of microbial contamination. Further, the endorsement of a one-hour exposure period does not appear to be science-based.
4. **Line 218 – Responsibility of Compounding Personnel:** Item 4 in this section states:

“To minimize the generation of bacterial endotoxins, water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation.” (Line numbers: 258-260)

It is good practice to carry through the compounding steps to final product without delay. The specified six-hour time limit appears neither to be science-based nor to consider whether the preparation has microbial-growth-promoting

properties. The holding period is product specific, and should be justified by knowledge of the product and supported by data. For example, a six-hour holding period would be too long for products that are growth promoting.

5. **Line 1460 – Sterility Testing:** This section states that:

“All high-risk level CSPs that are prepared in groups of more than 25 individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they are sterile (see Sterility Tests <71>) before they are dispensed or administered.” (Line numbers: 1461-1465)

The reference to “25 individual single-dose packages” appears not to be science-based. It may lead to a pharmacy compounding multiple batches consisting of fewer than 25 units of high-risk CSPs in order to avoid sterility tests. Sterility testing ought to be based on scientific data justified by knowledge of the product (e.g., the need to test a preparation with microbial-growth-promoting properties).

F. Storage conditions for CSPs require references

Line 1502 – Beyond-Use Dating: We are concerned with the instruction in the section **Determining Beyond-Use Dates** stating that:

“Compounding personnel who assign beyond-use dates to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to decide a conservative and safe beyond-use date and storage conditions.” (Line numbers: 1588-1592)

Specific authoritative references (e.g., ICH) need to be added to the chapter to instruct pharmacists on where they can find this information.

G. Line 417 – High-Risk Level CSPs – High-Risk Conditions: The shorter storage period established for high-risk products that are steam sterilized (NMT 24 hours at RT/ 3 days at refrigeration/45 days frozen; Line number: 438) appears to be based on an incomplete scientific rationale. Providing general information on the length of storage and acceptable temperature ranges that apply to all drug products, regardless of physicochemical properties, is not scientifically sound. We suggest removing the references entirely, or stating that the exact storage

conditions need to be based on the compounded products' physical and/or chemical characteristics and sensitivities (e.g., heat).

2. Language, Organization, Style, and Intent of Chapter

- A. **Language and Usage:** The Compendial Operations Staff, in preparing this letter, has observed that the chapter often uses the word "and" when "or" would seem to be correct [for example, see line number 439 ("*...and for 45 days in solid frozen state...*") and line number 1463 ("*...exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8°...*")] . It is recommended that this be brought to the attention of the USP technical editors for their review.
- B. **Organization:** Placing the section discussing the requirements of the **Quality Assurance Program** at the end of the chapter may imply that it is an afterthought or a low priority. This section is vital to the success of compounding activities and should be placed prominently at the beginning of the document. We recommend placing it after **Definitions** and before **Responsibility of Compounding Personnel**. (Line number: 217)
- C. **Style:** The chapter is very lengthy and involved, which diminishes its usefulness as a clear directive or requirement. One solution is to group all information on a topic in discrete sections (e.g., placing all environmental monitoring discussions in one section), which would provide easy reference and minimize confusion in locating information. Another suggestion is to provide lettered section headers that might allow for easier referencing. For example:
- A. Definitions of chapter terminology
 - B. Responsibility of compounding personnel
 - C. Single-dose and multiple-dose containers
- D. **Intent:** The terms "require," "shall," "should," and "must" are used interchangeably in the chapter, thus causing uncertainty as to what is a requirement and what is a recommendation. We recommend that USP also clarify whether the chapter is intended to be a "minimal standard" or a "gold standard" to which compounding pharmacies should strive to adhere. This will help pharmacists to understand whether the information contained in the chapter is required or merely recommended (see also **Comment 3**, below).

3. Appropriate Placement of Certain Standards in USP General Chapters Below 1000

We are mindful of USP's policy for determining whether a provision is mandatory, based on whether it appears in chapters above or below 1000 and on whether it is specifically referenced in a monograph or elsewhere in the USP (source: USP 29 *General Notices*):

"Articles recognized in these compendia must comply with the official standards and tests and assays in the General Notices, relevant monographs, and General Chapters numbered below 1000. General Chapters numbered above 1000 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no official standards, tests, assays, or other mandatory requirements applicable to any Pharmacopeial article unless specifically referenced in a monograph or elsewhere in the Pharmacopeia."

USP's policy regarding which USP provisions are mandatory and which are interpretive has a significant impact on industry practice, as well as on state and federal enforcement policies. Given CDER's significant concerns about certain ambiguities and scientific inaccuracies in the draft, CDER is concerned about their inclusion in Chapter <797>, which, under USP's policies, would make them mandatory.

In addition, the current <797> chapter frequently provides lengthy and detailed information, much like a "how-to" manual on recommended procedures and practices for sterile pharmaceutical compounding. In many instances, the specificity and detail in the chapter impose a mandatory and rigid design, control, and maintenance approach that does not allow for technological advances and does not account for the various pharmacy practice settings that prepare sterile pharmaceutical compounds.

For these reasons, much of the information in the draft is not appropriate as mandatory criteria. We recommend that, if retained, these provisions should be moved to a USP "interpretive" chapter on pharmacy compounding (i.e., one numbered above 1000). They will thus be viewed as recommendations rather than as requirements. If USP is receptive to this change, we would be happy to work with it to further specify the sterile compounding provisions that should be moved to an interpretive General Chapter numbered above 1000.

Topic II. Comments on the USP publication *USP <797> Guidebook to Proposed Revisions*; Section Entitled, "Enforceability and Recognition of General Chapter <797>":

Section – Introductory Paragraphs

1. First Paragraph
 - a. Sentence 2: Amend as follows: *"In this article, USP discusses its views on the enforceability and recognition of General Chapter <797> by the federal government and by the Boards of Pharmacy in selected states."*
2. Second Paragraph
 - a. Sentence 2: Amend as follows: *"Drug manufacturers are regulated primarily under the Federal Food, Drug, and Cosmetic Act (FFDCA), which includes several references to USP standards."* Also insert a footnote here with the following text: *"See, e.g., 21 U.S.C. §§ 351(a)(2)(C), 351(b), 352(e), and 352(g)."*
 - b. End of Paragraph: Amend as follows: Add the following sentence to the end of this paragraph: *"However, the FFDCA, through its regulation of drugs, also applies to drugs compounded by practitioners, as well as their practice, facilities, and procedures."*

Section – U.S. Food and Drug Administration (FDA)

3. First Paragraph. Amend as follows:

"In general, the FDA defers to the states with regard to pharmacies engaging in traditional pharmacy compounding. As the Director of the FDA's Center for Drug Evaluation and Research testified to Congress in 2003, the 'FDA recognizes that states have the direct ability to regulate pharmacy compounding and direct access to prescription records.' Although the FDA generally does not routinely inspect pharmacies engaged in traditional pharmacy compounding, it will inspect pharmacies and take enforcement action against compounded preparations that significantly violate the new drug, adulteration, or misbranding provisions of the FFDCA (e.g., they present quality, safety, or purity issues for patients)." Insert footnote here with the following text: "FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ['Pharmacy Compounding'], issued by FDA in May 2002."
4. Second Paragraph. Comment: FDA's enforcement approach to USP <797> is a function of the authority afforded by the FFDCA, not FDA's decision to defer to states for routine pharmacy regulation. Further, while FDA does contribute to the regulation of pharmacy compounding, in part, through its association with other entities, this paragraph gives

the misimpression that this is the only avenue through which FDA regulates pharmacies. Given these misunderstandings, we recommend deletion of this paragraph, except for the second sentence, which we propose to move to the first paragraph of this section, as noted above.

5. Third Paragraph. Amend as follows:

"The requirements of the FFDCa apply equally to all drugs, whether they are compounded drugs or manufactured drugs. Under the FFDCa, drugs that are recognized in official compendia, including the USP and the National Formulary (NF), are deemed to be adulterated if their strength differs from, or their quality or purity falls below compendial standards." [Insert footnote here with the following text: "See 21 U.S.C. § 351(b)."]
"The FFDCa also provides that drugs that are recognized in official compendia are deemed to be misbranded unless they are packaged and labeled as prescribed therein." [Insert footnote here with the following text: "See 21 U.S.C. § 352(g)."] *"Compendial drugs may also be subject to enforcement action by the FDA under other provisions of the FFDCa."* [Insert footnote here with the following text: "See, e.g., 21 U.S.C. § 351(a)."]

6. Fourth Paragraph. Amend as follows:

"Thus, while the FDA generally defers to the states to regulate the practice of pharmacy and other health professions, it takes a keen interest in the quality and safety of the compounded preparations that reach patients. The FDA will act with the states in investigating allegations of poor quality compounded drugs, but is willing and able under the FFDCa to act on its own initiative. The FDA intends to continue to work with the states, but if a state is unwilling or unable to participate, the FDA may choose to act unilaterally to protect the public health from compounded drugs that pose unreasonable risks."

We hope these comments will be helpful to USP and the Sterile Compounding Expert Committee. Please feel free to contact me at 301-796-1585 if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely,

Larry A. Ouder Kirk

Larry A. Ouder Kirk

Director

Compendial Operations Staff

Office of Pharmaceutical Science

Center for Drug Evaluation & Research



"Joe Grasela"
<joegrasela@san.rr.com>

01/04/2008 01:27 PM

To "CPHA Paige Talley" <ptalley@cpha.com>, "John Cronin"
<jcronin@fmglegal.com>, <anne_sodergren@dca.ca.gov>

cc

bcc

Subject title 16 comment

my comment to the board of pharmacy on title 16 is that title 16 should be made clear that physicians intending to compounding in their offices should follow the same laws. we are seeing much more of this lately.

Joe Grasela



"William Blair"
<BillB@mcguff.com>
01/14/2008 03:33 PM

To <anne_sodergren@dca.ca.gov>
<virgina_herold@dca.ca.gov>, "Dennis Ming"
cc <dennis_ming@dca.ca.gov>, <dan@grandpas-rx.com>,
"Steve Gray" <steve.w.gray@kp.org>, <klynch@cpha.com>,
bcc
Subject Title 16. Board of Pharmacy Proposed Language

Dear Ms. Sodergren,

I am recommending modification of the proposed regulations as follows:

Title 16. Board of Pharmacy Proposed Language

Current Proposed Language:

§1735.1. Compounding Definitions

(b) "Potency" means active ingredient strength within +/- 10% of the labeled amount.

Recommended Language:

§1735.1. Compounding Definitions

(b) "Potency" means active ingredient strength within the specifications listed in a monograph of an official pharmacopoeia, e.g., USP/NF, British, European, or Japanese. If the compounded product is not listed in one of these pharmacopoeias, then the specification range shall be +/- 10% of the labeled amount, or a specification range developed by the pharmacy based on knowledge and experience of the pharmacist.

Rational: There are potency ranges in the USP/NF, British Pharmacopoeia, European Pharmacopoeia, or Japanese Pharmacopoeia monographs that are different than +/- 10%. The USP/NF monograph, British Pharmacopoeia monograph, European Pharmacopoeia monograph or Japanese Pharmacopoeia monograph should be followed when there is such a monograph. If there is no such monograph, then the pharmacist may default to the +/- 10% range unless knowledge and experience shows that a more narrow or broader range is required. (It is recommended that the specification range and source of the range be documented in the master formula record.)

Current Proposed Language:

§1751.2. Sterile Injectable Labeling Requirements.

In addition to existing labeling requirements to the labeling information required under Business and Professions Code section 4076 and section 1735.4, a pharmacy which compounds sterile injectable products shall include the following information on the labels for those products:

(b) Name and concentrations of ingredients contained in the sterile injectable product.

Recommended Language:

§1751.2. Sterile Injectable Labeling Requirements.

In addition to existing labeling requirements to the labeling information required under Business

and Professions Code section 4076 and section 1735.4, a pharmacy which compounds sterile injectable products shall include the following information on the labels for those products:

- (b) Name of all active and inactive ingredients contained in the sterile injectable product.
- (c) Concentration of all active ingredients.

Rational: It is not possible to list the concentrations of some of the inactive ingredients that are used to adjust pH since the pH may vary depending on the manufacturer of the active pharmaceutical ingredients. The amount of the pH adjusting reagent may vary from batch to batch.

Please call me if you have any questions.

Very best wishes,

William J. Blair, Pharm.D., MBA
Director of Pharmacy Services
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., Ste. 142
Santa Ana, CA 92704
Telephone: 877-444-1133
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"Dan Wills"
<dan@grandpas-rx.com>

01/15/2008 05:18 PM

Please respond to
<dan@grandpas-rx.com>

To <anne_sodergren@dca.ca.gov>

cc

bcc

Subject Comments about the compounding regulations.

History:

📧 This message has been forwarded.

Dan Wills, MBA
Grandpa's Compounding Pharmacy
7563 Green Valley Rd
Placerville, CA 95667
Phone: 530-622-2323
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Cell: 530-903-6079



Compounding comments 1-11-08.doc

January 11, 2008

Anne Sodergren
Legislative Coordinator
California State Board of Pharmacy
1625 N. Market Blvd., N 219
Sacramento, CA 95834

Dear Ms. Sodergren,

In regard to the proposed language for the compounding regulations I have several comments. I will separate them into categories of importance.

Critical

CCR 1751.7(a) The sentence that says, "The end product shall be examined on a periodic sampling basis as determined by the pharmacist in charge to assure that it meets required specifications." has been removed. I assume it was to try to clean up the language a bit and 1751.7(a)(5) was added. This sentence states that a quality assurance program will include: "End-product testing and process validation procedures."

I can interpret this to mean one of two things. It could still mean that our policies and procedures shall include a policy outlining a sample based testing program as was originally in the law. The other interpretation is very problematic and will harm the public and put pharmacies at risk of being closed down or at least stopping all Class III sterile compounding. This interpretation would be that there shall be end product testing of all sterile compounds.

1751.7(d) allows for periodic testing of batch-produced sterile to sterile compounding (Class I), so this either creates an exemption from this interpretation, or goes to show that end product testing on all sterile compounds is not what is intended.

1751.7(c) says that all batch produced items need to be tested for sterility and pyrogens. When we were writing the original language for this in the committee, we all understood that a batch is when enough product was made to fill several prescriptions. When you take these two paragraphs together it is clear what is to be done with batch-produced sterile compounds. What is no longer clear to me is what the requirement is for testing when the sterile product is produced for an individual prescription.

When I look at the Initial Statement of Reasons I find:

Amend 16 CCR 1751.7 – Sterile Injectable Quality Assurance and Process Validation

This section is amended to require that end-product testing and process validation procedures are included in the quality assurance program and clarifies that the pharmacist-in-charge is responsible for determining periodic testing.

This sounds to me like it is not a rewording, but a new requirement of testing. I am deeply troubled at this thought and hope I am wrong in this interpretation. First off, this type of new requirement has never been discussed in public that I am aware of and I have been at most of the meetings. Secondly, testing of every product was not the original intent of the sterile regulations in the past. It had been discussed at length and determined that it was too cost prohibitive and would restrict public access to life saving or enhancing medications. To test for sterility and pyrogens costs around \$150 depending on the lab. There is also the cost of shipping the sample. We do a sterility test in-house on every sterile item we make, but it does not have the same credibility as an outside test nor is it as complete. To do a true USP qualified sterility test is cost prohibitive on all sterile compounds.

So the bigger question is whether or not public access to sterile compounding is needed. The legislature thought so when they passed the law requiring the Board to make the sterile compounding regulations. The first law that was put forth would have restricted access and they decided not to do that. They instead decided to ask the Board to make regulations that would assure access in a safe way. I believe the Board did that and have even testified of that to some other government committees. The change of this language could again place unneeded restrictions on public access to sterile drugs.

Therefore, I suggest putting the language back in that assures periodic testing of sterile compounds is allowed under State Law. Otherwise, even if the change was meant to just clarify, it might be misinterpreted by somebody in the future such as the FDA.

Important

This has been brought up in the past and the intent of the rule has been stated in committee meetings. 1735.1(C) defines quality as “the absence of harmful contaminants, including filth, putrid, or decomposed substances, and absence of active ingredients other than those noted on the label.” The licensing committee has do a great job in refining this particular definition. I would add one more refinement to make it a little more clear. I am not concerned with how we interpret this phrase now, but how it might be interpreted in the future. If I were anti-compounding and wanted to shut down a store, I could use this phrase to shut down all compounders. All I would have to do is find a small amount of a contaminant that has been found harmful in large doses and say that there is a harmful contaminant in the product and shut the pharmacy down. For example, water has been found to be harmful in large doses. Recently in California, a lady died from drinking too much. So if I were to find water in a product, I could claim it is harmful. I know that is an extreme case that would not actually be used because it is too ridiculous. However, the principle is still a possibility.

The air we breath contains 100,000 foreign particles including bacteria, fungus, viruses, etc. per cubic foot of air. It would be impossible, to make a product in non-sterile conditions that would not have the possibility of containing one of these contaminants. So

for the aggressive enforcer, this would be a cakewalk to find one. Even in sterile compounding, there are pyrogens which can be harmful. The way the FDA, and USP have regulated these is to say that a sterile product should be non-pyrogenic, which does not mean pyrogen free, but means the levels are within a range that would not cause a fever. I would like to see something similar added to this phrase that would show the intent. Again, I am not worried about the intent of the current Board, but in the future the make-up of the Board will change. It is this change I am trying to anticipate. I have suggested changing the term from harmful contaminants to harmful levels of contaminants in the past. That was rejected at the time. So here are two other ideas.

1. Quality means the absence of contaminants, including filth, putrid, or decomposed substances in harmful amounts.....
2. Quality means the absence of contaminants, including filth, putrid, or decomposed substances in harmful concentrations.....

Or, perhaps it could be publicly acknowledged that this is the intent of the law so that in the future if there is a question, this acknowledgement could be referred to.

Clean up #1

1735.2(c) Says that with two exceptions no drug product shall be made without the prior receipt of a prescription either written or oral. The next sentence says, "Where approval is given orally, that approval shall be noted on the prescription prior to compounding." I do not believe this last line is needed. 1735(c) says that compounding does not include making something that is commercially available except in small quantities where there is a specific documented medical need. So when a pharmacy needs to make something that is essentially a copy of an available drug, documentation is already required to show why it must be compounded. If the doctor and pharmacist have already discussed this need then the doctor will know that it will be compounded.

If on the other hand, he is prescribing something that is not available, then he will also know that the only way he can get it is if it is compounded. Therefore, he again knows that he has ordered a compound. Based on this, there is no need to document that the order for a compound is indeed a compound.

However, if this is left in, you will be requiring the pharmacist to document a known fact and subjecting them to more work and unneeded regulation.

Clean up #2

1751.5 (3) Says that if a person can't get their jewelry off, then they should wash thoroughly and cover it with a sterile glove. Why does the glove have to be sterile when the rest of the time it should be a low shedding glove (1751.5 (5)). Standard procedures now a days is that the glove needs to be disinfected between each procedure and changed every half hour. In this case, a sterile glove doesn't add anything to the cleanliness of the procedure.

Clean up #3

1751.6 (c) Says that the employee training records for sterile compounding are to be saved for three years beyond their period of employment. Yet in all other places in these regulations, records are to be kept for three years period (See 1761.6(e)(2), 1751.1(c), 1735.3(d)). What is the benefit of keeping those records longer than the others? If a person works at a store for 30 years then the store must maintain those particular training records for 33 years when all the rest were thrown away 30 years earlier. Even the re-assessments are only kept for 3 years (1761.6(e)(2)).

Final thoughts

I really appreciate the opportunities and patience the Board and Staff have had through this process. It has been difficult and you have all done well. I also looked at the revised self evaluation and see that it has been cleaned up well and is basically flawless. Good job. I believe the Board has truly acted in the best interest of the public, by ensuring them with access to safe medicines from qualified personnel.

Sincerely,

Dan Wills, MBA
Manager

Comments from Victoria Ferrarest, PharmD, and Barbara Burgess, RN, Pathways Home Health & Hospice.

1. We are requesting that you add an additional item to the definition of what compounding is not:

“Placement of patient’s legally prescribed medication from the labeled pharmacy container into an oral dosing syringe or a medication organizer to assist the patient in self-administration.”

Board’s Response

The request is outside the scope of the regulation. The regulation is defining compounding and exceptions to that definition when it occurs in a pharmacy. The above recommendation is action that occurs after the prescription has been dispensed by the pharmacy.

Comments from Dawn Benton, Interim Executive Vice President, California Society of Health-Systems Pharmacists.

1. CSHP expressed concern that the proposed language of Article 4.5 “Compounding” language which also pertains to Article 7 “Sterile Injectable Compounding” will negatively impact the preparation of one-time, and immediate-need injectable products. More specifically, CSHP is concerned that the added documentation requirements will delay the preparation and delivery of these urgently needed medications in acute care facilities without any additional benefits to patient safety and care.

Board Response

The board disagrees that the proposed regulation will place an additional burden on acute care facilities without any additional benefits to patient safety and care. Specifically, in an acute care setting, the regulation proposal allows for one-time preparations to be documented in the pharmacy’s copy of the patient’s chart order. Further, immediate-need injectable products are either compounded in advance with a “master formula” and as such the components of the product are already known, or individually compounded similar to one-time preparations, in which case the pharmacy’s copy of the patient’s chart order will satisfy the documentation requirement.

2. Currently, emergency medications are prepared in the pharmacy and labeled with adequate information to assure patient safety and recall should such a medication be recalled in the next few hours during the administration of the medication. Additional record keeping or

generation of a pharmacy specific lot number for each IV syringe, Piggyback or Large Volume Parenteral compounded does not serve the patient. It only delays medication preparation and delivery to the patient and places an additional burden on the pharmacy.

Board Response

We appreciate the concerns addressed by the CSHP. The intent of the regulation proposal is to improve patient safety. The board would like more specific information about how the “common practice” for a pharmacy in an acute care facility allows for the recall of a medication. The board will consider an amendment that strikes a better balance between the need of pharmacy operations in an acute care setting and that of patient safety if one is offered.

3. In the interest of patient safety, CSHP recommends the following amendment clarifying immediate need sterile injectable products in acute care facilities

1751.1 (b) Pharmacies in an acute care facility compounding sterile injectable products for the immediate needs of a patient may record required components of section 1735.3 on the patient-specific product label instead of records maintained in the pharmacy unless otherwise specified below.

1. Immediate need is defined as medication administration is completed within 24 hours.
2. Master formula record including equipment used in compounding the drug must be readily retrievable in the pharmacy.
3. Manufacturer or supplier and lot number of each component must be readily retrievable in the pharmacy.
4. Pharmacy assigned reference or lot number for the compounded drug is not required.

Board Response

We appreciate the CSHP offering a proposed solution. However, the language proposed is unclear. Board staff will seek additional clarification on the intent to the proposed language and will offer alternative language for board consideration.

4. In addition for clarity we suggest the following addition to Section 1735.3. Records of Compounded Drug Products.

Section 1735.3 (a) Except as specified in Section 1751.1, for each compounded drug product, the pharmacy records shall include:

1. The master formula record.
2. The date the drug was compounded.
3. The identity of the pharmacy personnel who compounded the drug product.

4. The identity of the pharmacist reviewing the final drug product.
5. The quantity of each component used in compounding the drug product.
6. The manufacturer or supplier and lot number of each component.
7. The equipment used in compounding the drug product.
8. A pharmacy assigned reference or lot number for a compounded drug product.
9. The expiration date of the final compounded drug product.
10. The quantity or amount of drug product compounded.

Board Response

We appreciate CSHP offering alternative language. Board staff will require clarification on the intent of the alternative language provided in Comment 3 before we are able to determine the necessity and appropriateness of this recommendation.

Comments from Michael M. Levy, Jr. Director, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research, Food and Drug Administration.

1. While the FDA supports some of the provisions of the proposed regulations as appropriate limitations on compounding, FDA is concerned that some of the proposed regulations would purport to legalize conduct that runs afoul of the factors in our current CPG and would be inconsistent with FDA's enforcement policy for compounded drugs. This concerns us because the proposed regulations would not provide a safe harbor against federal enforcement.

Board Response

The proposed regulation is not intended to serve as a safe harbor against federal enforcement. Pharmacies are required to comply with state and federal law, and where the two are not in concert, the more stringent requirements apply. The proposed regulation defines the minimum requirements under which a pharmacy may compound. The FDA Compliance Policy Guide (CPG) may define best practices, but is not a requirement of state or federal law.

2. The proposed regulation appears to permit compounding of commercially available drug products in small quantities based on a documented medication need. The FDA suggests that the language "that is commercially available in the marketplace or" be struck. Compounding copies of commercially available, FDA-approved drugs is not permitted by the Federal Food, Drug and Cosmetic Act (FDCA) and is at odds with the FDA's enforcement policy under the CPG.

Further, FDA believes that pharmacists should compound near copies of commercially available, FDA-approved drugs only when the drug is needed to produce for a patient a significant medical difference that is not afforded by a commercially available, FDA-approved drug product. Absent this medical need, such compounding is inappropriate, even when it occurs in small quantities.

Board Response

The board agrees that compounding a commercially available product is inappropriate in most cases which is why the regulation proposal prohibits the compounding of a commercially available drug product in the marketplace **unless** it is justified by a specific, documented, medical need. It would be contrary to public protection to not allow such compounding on an emergency basis.

3. FDA suggests that the definition also include other elements of quality mentioned in the FDCA, such as the requirement that a drug representation itself as a drug the name of which is recognized in the official compendium must meet the compendial standards. 21 U.S.C. §351(b). For non-compendial drugs, the drug should meet the quality standards its purports to possess. 21 U.S.C. §351(c).

Board Response

The definition used in 1735.1 of the proposed regulation is based upon the Sherman Food, Drug and Cosmetic Act. Furthermore, the language in its current form meets the board's consumer protection mandate. We do not believe that meeting the compendial standards is necessary as it places an undue burden on pharmacies that are compounding medicines for patient care. This proposal is not designed to replace or supercede federal law or requires, but rather to work in concert with such requirements.

4. FDA is concerned that the proposed regulation (specifically 1735.2(c)) may permit activities that go beyond traditional pharmacy compounding and would implicate several factors in the CPG including:
 - whether a firm compounds drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;
 - whether a firm compounds drugs for third parties who resell them to individual patients or offers compounded drugs at wholesale to other state licensed persons or commercial entities for resale; and
 - whether a firm compounds large quantities of standardized drugs.

Board Response

The board shares the concern of FDA but believes that no amendment is

necessary. The proposal clearly defines the conditions under which anticipatory compounding can occur.

5. FDA recognizes that it may be appropriate in some circumstances for a pharmacist to compound minimal quantities of drugs solely for administration in a practitioner's office when commercially available, FDA-approved drugs cannot meet the medical needs of a specific patients of the practitioner. However, FDA is concerned that the proposed regulation does not include sufficient limitations and safeguards and therefore is potentially inconsistent with FDA's enforcement policy regarding compounded drugs.

Board Response

The board shares the concern of FDA, but disagrees that the proposed regulation does not include sufficient limitations and safeguards. The board respectfully disagrees that the proposed language does not sufficiently address limitation. The language as proposed clearly defines the limitations for compounding for dispensing by a practitioner. Also, absent any specific examples of alternate language to enhance safeguards, the board deemed those included in proposed 1735.2(c) in the best interest of consumer protection.

6. FDA proposed that the specific pharmaceutical standards for integrity, purity, quality and strength be articulated in the regulations.

Board Response

We do not believe that such definitions are necessary. Why??

7. FDA also suggests that the regulations provide that the pharmacy maintain documentation identifying the patients to whom the compounded drug was administered. Methods for identification could include a practitioner's agreement to identify to the pharmacy the patients who receive the compounded drug.

Board Response

The suggested amendment is not necessary. Pharmacy law already requires a pharmacy to maintain all records of disposition, which would include a compounded medicine dispensed pursuant to a prescription. The pharmacy is not responsible for maintaining records on medicines dispensed in a practitioner's office.

8. FDA believes that the proposed regulation could be strengthened with respect to the provision of compounded drugs to practitioners by prohibiting the pharmacy or pharmacist from compounding drugs for practitioners that will be sold by the practitioner to other persons or entities (other than the patient being administered the drug.)

Board Response

The suggested amendment is unnecessary. This proposal adequately defines the conditions under which a pharmacy can compound drugs for practitioners. Further, the board does not have jurisdiction over such practitioners and would be unable to enforce non-compliance with the proposed amendment.

9. FDA believes that requiring that labels of drugs compounded for practitioners who will be administering the drug to patients be labeled with the statement "For Office Use Only – Not for Resale", could strengthen the proposed regulation.

Board Response

The suggested amendment is unnecessary. The board does not have jurisdiction over such practitioners and would be unable to enforce non-compliance with the proposed amendment.

10. FDA believes that a general beyond use date, as provided for in proposed CCR 1735.2, of no more than 180 days for compounded drug products may not be supported by data or by recognized reference and continue that the compendial beyond use dates appear to reflect the type of formulation and therefore may provide a more appropriate beyond use date.

Board Response

The board believes that the language as proposed appropriately and sufficiently addresses the determination a pharmacy must use to designate a "beyond use date." Specifically, the proposed language provides in specific terms that the beyond use date cannot exceed 180 days. The proposed language, however, also allows a longer date if it is supported by stability studies. The proposed language further specifies that a shorter "beyond use" date must be used to be consistent with the shortest expiration date of any component in the compounded drug product.

11. Proposed section 1735.2(j) describes the annual completion by the pharmacist-in-charge of a self-assessment form for compounding pharmacies. FDA understands that the form will not replace an inspection, but instead will be reviewed at inspections. FDA agrees that the form cannot take the place of the required procedures.

Board Response

The board appreciates FDA's understanding and value of the self-assessment form. The board will not use the self-assessment form to

replace inspections. Business and Professions Code section 4127.1 requires the board to complete annual inspections of all pharmacies licensed pursuant to this section.

12. FDA notes that there are no provisions for other types of sterile preparations, such as ophthalmic preparations. Such preparations are required to be sterile, and pharmacies that prepare such preparation and other sterile preparations should follow appropriate practices to ensure product sterility.

Board Response

While the board does not disagree with the above statement and recognizes the need for regulation in this area, the preparation of other types of sterile preparations, such as ophthalmic preparation, are outside the board's jurisdiction.

13. FDA suggests that the written master formula record described in §1735.2(d) be amended to include two additional items: the source of the active pharmaceutical ingredient and the lot number.

Board Response

The board agrees that this information about the source of the active pharmaceutical ingredients and lot number is important. Records of each of these items is included in §1735.3 and must be included for each compounded drug, not just as part of the master formula as suggested by FDA.

14. Proposed §1735.3(c) states that chemicals, bulk drug substances, drug products and components for compounding be obtained from reliable suppliers. Consistent with the policy articulated in our CPG, FDA suggests that such reliable supplier provide written assurance that each lot of drug substance has been made in an FDA-registered facility.

Board Response

The board does not believe the additional record keeping requirements mandate is necessary, however, does agree that that such confirmation would be good policy as articulated in the CPG. FDA is responsible for registering and ensuring the compliance of such suppliers. Compliance with such a requirement would be under the purview of FDA, not the board.

15. Section 1735.5(c) describing the compounding policy and procedure manual should include procedures for maintaining records and investigating complaints.

Board Response

This recommendation is not necessary as the proposed language adequately defines the components of the quality assurance plan policies and procedures, which would include investigating complaints.
Retention??

16. Section 1735.6 describing "compounding facilities and equipment" should include a provision on the methods of cleaning and disinfecting equipment and facilities prior to and after compounding.

Board Response

This suggested change is not necessary and proposed section 1735.5(a) requires the documentation of the facilities and equipment cleaning requirements as part of the written policies and procedure manual.

17. Section 1751.1(b) should require a file on complaints.

Board Response

This suggested response is not necessary as the proposed language specifies that the records shall be in a readily retrievable form for at least three years -- how the pharmacy chooses to comply with this requirement is a business decision.

18. Section 1751.4(d) requires that surfaces in designated areas be disinfected weekly. The agency is concerned that disinfecting these areas weekly may be insufficient, and we refer you to our comments on the United States Pharmacopeia in its Chapter 797.

Board Response

The comments suggested by FDA are outside the scope of this proposal as it is existing law. Further, the language in its current form meets the board's consumer protection mandate. Neither existing law, nor this proposal, can preempt federal law and is designed to work in concert with federal requirements. FDA is charged with enforcing federal requirements.

19. Section 1751.5(a) states that gowns and gloves shall be worn when preparing cytotoxic agents. FDA suggests that such attire should be worn when compounding other sterile drugs.

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

20. Proposed section 1751.5(b) states "...when compounding sterile products

from one or more non-sterile ingredients the following standards must be met..." FDA suggests striking the phrase "from one or more non-sterile ingredients" since the standards should also apply when compounding sterile products using sterile ingredients.

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

21. Section 1751.5(b)(3) states that when compounding, sterile gloves should be worn when jewelry cannot be removed. FDA suggests that sterile gloves should always be worn when compounding sterile preparations.

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

22. FDA is uncertain why proposed §1751.5(c) states that the provisions of §1751.5(b) do not apply if a barrier isolator is used to compound sterile injectable products. Some of the requirements in §1751.5(b) – such as removal of jewelry – may in fact apply when a barrier isolator is used. FDA suggests the revision of §1751.5(c) to clarify which provisions of §1751.5(b) would apply.

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

23. FDA suggests that proposed §1751.7(a)(3) be revised to add "or complaint" to the end of the sentence, so that the sentence would read"

"(3) Actions to be taken in the event of a drug recall or complaint."

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

24. FDA suggests that §1751.7(b) be amended to add "compounding" before the term "technique" that appears in the second line of this section. If this amendment is accepted, the first sentence of §1751.7(b) would read"

"Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on compounding technique before being allowed to prepare sterile injectable products."

Board Response

The board is not proposing any changes in this requirement. As such, the comments suggested by FDA are outside the scope of this proposal as it is existing law.

Comments from Joe Grasela

1. Title 16 should be made clear that physicians intending to compound in their offices should follow the same laws.

Board Response

Although is comment submitted comment is unclear as to what the comment is specifically addressing, the board does not have jurisdiction over physicians. Such mandates would need to be adopted and enforced by the Medical Board of California.

Comments from Counsel

Discussion Items/Suggested Changes to Compounding Regulations as Noticed for Comment by 12/31/07

In the following, I have attempted to compile a few minor suggestions/discussion items that have been lingering for a while and/or were prompted by comments made at the last meeting (and/or in the more recent submission by CSHP regarding immediate-use patient-specific compounds).

- (1) Consider changing § 1735.1, subd. (c) to read:

(c) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, and the absence of active ingredients other than those noted on the label.

- (2) Consider changing § 1735.2, subd. (j) to read:

(j) Prior to allowing any drug product to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment form for compounding pharmacies developed by the board (form 17m-39 rev. 10/07). That form contains a first section applicable to all compounding, and a second section

applicable to sterile injectable compounding. The first section must be completed by the pharmacist-in-charge before any compounding is performed in the pharmacy. The second section must be completed by the pharmacist-in-charge before any sterile injectable compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start of a new pharmacist-in-charge, and within 30 days of the issuance of a new pharmacy license. The primary purpose of the self-assessment is to promote compliance through self-examination and education.

(3) Consider changing § 1735.3, subd. (a)(6) to read:

(6) The manufacturer and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted.

(4) There is extra underlining in § 1735.5, subd. (c)(1)

(5) Consider changing § 1735.6, subd (c) to read:

Any equipment used to compound drug products for which calibration or adjustment is appropriate shall be calibrated prior to use to ensure accuracy. Documentation of each such calibration shall be recorded in writing and these records of calibration shall be maintained and retained in the pharmacy.

(6) In § 1751, subd. (b)(6), it should read “in accordance with” rather than “in accordance in”

(7) There is missing underlining in § 1751, subd. (c)

(8) I was intending to respond to CSHP’s comments/request for an exemption, and have some ideas about what they might want, but since their comments/proposed language strike me as internally inconsistent (i.e., I do not understand exactly what they want), unless somebody else understands better than I do what they want, I guess we need to hear from them orally.

(9) In § 1751.3, subd. (c), where did the additional (underlined) language come from? It’s quite possible that was my addition, but I do not recognize it (and it’s not a complete sentence). May want to replace this last sentence with: “The written policies and procedures shall describe the pharmacy protocols for cleanups of spills in conformity with local health jurisdiction standards.”

(10) In § 1751.5, subd. (e), why is there partial underlining?

(11) In § 1751.7, subd. (a), I would delete subpart (5) and undelete the sentence in the stem of subdivision (a) that begins “The end product shall be examined on a periodic sampling basis . . .”

(12) In § 1751.7, subd. (d), is that partial underlining intentional?

(13) On the Self-Assessment Form itself, I would change the first paragraph(s) to read:

California Code of Regulations section 1735.2 requires the pharmacist-in-charge of each licensed pharmacy that compounds or seeks to compound drug products to complete the following self-assessment of pharmacy compliance with federal and state pharmacy law.

The following form contains a first section applicable to all compounding, and a second section applicable to sterile injectable compounding. The first section must be completed by the pharmacist-in-charge before any compounding is performed in the pharmacy. The second section must be completed by the pharmacist-in-charge before any sterile injectable compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start of a new pharmacist-in-charge, and within 30 days of the issuance of a new pharmacy license. The primary purpose of the self-assessment is to promote compliance through self-examination and education.

The applicable sections of the self-assessment must be completed in their entirety. The form may be completed online, and then printed and retained in the pharmacy. On each occasion that a self-assessment is required, a new self-assessment form is required; do not copy a previous self-assessment in whole or in part.

[Then the two bolded paragraphs/sentences currently on the form.]

(14) I would more clearly sub-divide the self-assessment form into two "sections," the first for "All Compounding Practices," and the second for "Sterile Injectable Compounding."

(15) There was something on the self-assessment form that somebody at the last meeting pointed out was missing (a requirement that was missing from a checklist, I think). Unfortunately, it has escaped my memory what that was. Hopefully, somebody else will remember.