October 28, 2003

To: James C. Boylan, Ph.D., Chairperson
Executive Committee
General Policies and Requirements Division, GPR
United States Pharmacopeia Council of Experts

Subject: Report of Parenteral Products – Compounding and Preparation Committee (known informally as "The Sterile Compounding Committee")

From: David W. Newton, Ph.D., Committee Chairperson

Dear Jim, Fellow GPR Chairpersons, and Sterile Compounding Committee Colleagues:

I regret that neither I nor vice chair person David Driscoll are able to attend the November 17, 2003 GPR Division Executive Committee meeting. In lieu thereof, I submit this report on behalf of my Sterile Compounding Committee colleagues: Kathleen R. Anderson, Pharm.D. (FDA liaison); Samuel C. Augustine, Pharm.D.; Gayle A. Brazeau, Ph.D.; David F. Driscoll, Ph.D., Vice Chair; Donald J. Filibeck, Pharm.D.; Kenneth L. Hughes, R.Ph.; Claudia C. Okeke, Ph.D. (USP liaison); Lawrence A. Trissel, R.Ph.; and James W. Wilson, R.Ph.

Recommendations

_ The Council of Experts Committee currently titled "Parenteral Products – Compounding and Preparation" should be officially retitled "Sterile Compounding"

_ USP should maintain an expert committee of pharmacists with substantial sterile compounding experience with the charge to ensure that Chapter <797> Pharmaceutical Compounding – Sterile Preparations, or whatever USP document that <797> may become, retains safe and practicable content, which compounders will apply; not neglect. Every member of the 2000-present Sterile Compounding Committee is a pharmacist.

_ USP preparation and testing requirements for compounded sterile preparations should not become commensurate with those for manufactured sterile drugs and nutrients produced in large lots.[a, b] Such requirements could (1) deprive effective and humane care to unique patients whose therapists prescribe special non-manufactured drug and nutrition therapy in limited amounts and durations, and (2) create marketing advantage for large providers of compounded sterile preparations.

_ USP employee leaders should urgently determine an efficient and inexpensive procedure for pharmaceutical compounders and state boards of pharmacy to access or possess all USP chapters, monographs, and other information related directly to pharmaceutical compounding practice.

June – October, 2003 Events and Related Comments

USP chapter <797> published in the July-August, 2003 *Pharmacopeial Forum* shall become official January 1, 2004. During summer 2003, Dave Newton was an invited guest at meetings of the USP Analytical Microbiology, and Industrial Parenterals Expert Committees. The membership of those Committees is predominantly industrial and federal regulatory pharmaceutical scientists, some of whom (a) criticized <797> for insufficient or absent standards, (b) questioned the need for sterile compounding at all, and (c) perceived <797> as promoting the practice of sterile compounding.

The first concise U.S. information sources specifically for sterile pharmaceutical compounding were ASHP's 1993 Guidelines[c] and USP's 1995 Chapter <1206> Sterile Products for Home Use.[d] Long before those documents, physicians relied on local patient-dedicated, risk-taking hospital pharmacists to compound injections that were needed to improve medical and surgical care, for example, phenytoin and nitroglycerin,[e] which subsequently became manufactured products. Sterile compounding preceded, and would proceed in the absence of, any pertinent USP chapters and monographs.

In early October, 2003 Dr. Okeke received from a pharmacy compounding business a 12-paged list of 30 recommended changes to <797> as published in July-August, 2003 *Pharmacopeial Forum*. Requests to alter <797> may be expected to range from more lenient to more rigorous requirements, which forecast the USP norm of continual revision – "The road to success is always under construction."

November, 1997-April, 2002 Events

The impetus to transform <1206> to a chapter numbered less than 1000, i.e., from informational to FDA-enforceable status, stemmed from FDA's July 13 and 14, 2000 Pharmacy Compounding Advisory Committee meeting. That meeting resulted in FDA's August, 2001 Concept Paper pertaining to section 127 in the 1997 FDA Modernization Act or FDAMA, from which the following is a verbatim excerpt, excluding content in { } added by Dave Newton:

"FDAMA section 127 amended the {1938} Federal Food, Drug, and Cosmetic Act (the act) by adding section 503A (21 U.S.C. 353a), which governs the application of Federal law to pharmacy compounding. Under section 503A(a) of the act, a compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. "Compounded drug products are exempt … from three key provisions of the act…(1) Adulteration provision of section 501(a)(2)(21 U.S.C. 351(a)(2)(B)) (current good manufacturing practice (CGMP) requirements); (2) misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (labeling of drugs with adequate directions for use); and (3) new drug provision of section 505 (21 U.S.C. 355) (…use of drugs under … INDs … NDAs …. ANDAs). … drug products that "present demonstrable difficulties for compounding that reasonably demonstrate adverse effect on the safety or effectiveness of that drug product" (section 503A(b)(3) of the Act) {include}… All sterile products that are compounded under procedures other than those described in Chapter 1206 ["Sterile Drug Products for Home Use"] of the United States Pharmacopeia (USP)"[f]

On April 29, 2002, the U.S. Supreme Court declared section 503A of FDAMA invalid in its entirety, because it "contained unconstitutional restrictions on commercial speech (i.e., prohibitions on soliciting prescriptions for and advertising specific compounded drugs)."[g]

Summary of 2000-2003 Activities

The challenging process to transform <1206> to current <797> began in fall, 2000 and culminated with two 2-day full attendance meetings in Rockville, MD in fall, 2002 (one during the sniper attacks in October). The results of this revision process were published in the following *Pharmacopeial Forum* issues:

Vol. 28(2) [Mar.-Apr. 2002]:498-534.
Vol. 29(3) [May-June 2003]:750-809.
Vol. 29(4) [July-Aug. 2003]:940-965.

During summer, 2003 USP laboratory renewed interest in studying glycerin and hydrochloric acid injections monographs first submitted in 2001 by the Sterile Compounding Committee.

Prospects for 2004-2005

The Sterile Compounding Committee will have at least one meeting on a yet to be determined 2004 date to address comments received regarding changes to <797>, and consider sterile compounding monographs.

Footnotes

[a]Appendix. Selected Attributes of Compounded *versus* Manufactured Drugs.

Attribute	Compounded	Manufactured
direct distribution is to	patients and prescribers	pharmacies and wholesalers
therapeutic paradigm	match drug to patient	match patient to drug
public health risk from gross contamination or ingredients errors	small: few people exposed concurrently	large: many people exposed concurrently
history	• since unrecorded BC era • monographs dominated first USP in 1820; USP renewed activity in 1993	• since 1800s • standards added and increased in USP during and after WW II, e.g., 1942 Injections, and 1975 solid oral dosage forms dissolution test
main legal regulation	states' pharmacy boards and practice acts	U.S. FDA

[b]Janet Heinrich, Director, Health Care-Public Health Issues, U.S. General Accounting Office, October 23, 2003 report titled, State and Federal Oversight of Drug Compounding by Pharmacies. "The agency [FDA] recognized in its brief…in 2002 Supreme Court case…that applying FDCA's [Food, Drug and Cosmetic Act] new drug approval requirements to drugs compounded on a small scale is unrealistic – that is, not …feasible to require drug compounding pharmacies to undergo testing for new drug approval process for drugs compounded to meet the unique needs of individual patients." http://www.gao.gov/new.items/d04195t.pdf. Accessed 10-28-2003 by Dave Newton.

[c]ASHP technical assistance bulletin on quality assurance for pharmacy-prepared sterile products. *American Journal of Hospital Pharmacy*. 1993; 50 (November):2386-98.

[d] Evolution of the United States Pharmacopeia Chapter <1206>: "Sterile Preparations – Pharmacy Practices." *International Journal of Pharmaceutical Compounding*. 2001; 5 (July/August): 265-7.

[e] • Phenytoin Injections: From Compounding to Cerebyx. *International Journal of Pharmaceutical Compounding*.2002; 6 (November/December): 410-3.

• Nitroglycerin Injection (letter). *American Journal of Hospital Pharmacy*. 1970; 27 (November): 883

[f] www.fda.gov/cder/fdama/difconc.htm, FDA Concept Paper: Drug Products That Present Demonstrable Difficulty for Compounding Because of Reasons of Safety or Effectiveness. Accessed 10-27-2003 by Dave Newton.

[g] http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html. Accessed 10-27-2003 by Dave Newton..

This document was originally distributed October 28, 2003 via email attachment from Dave Newton to Jim Boylan, Loyd V. Allen, Jr.; and Dave's Sterile Compounding Committee colleagues.