

USP <797>

PHARMACEUTICAL COMPOUNDING – STERILE PREPARATIONS:*

Some History and Highlights

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Pharmaceutics Section AACP Annual Meeting
Seattle, WA July 11, 2010

- * <797> First official Jan 1, 2004 in USP 27:2350-70
- <797> First revision Jun 1, 2008 in USP 31 2nd Suppl.:3700-34

- ** Professor, Dept. Biopharmaceutical Sciences
Shenandoah University Winchester, VA dnewton@su.edu
- Chairman 2000-2005 and 2005-2010
Sterile Compounding Comm. (SCC or SCEC); USP Council of Experts†

†Council of Experts consists of USP committee chairs elected every five years
by USP Convention Delegates; chair persons are limited to two consecutive terms.

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Sterile compounding may not look this bad,
but some results can be as bad as this looks.



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<797> Raison d'être

Jul 2000 FDA Pharmacy Compounding Advisory Comm. : Products that "present demonstrable difficulties for compounding ... all sterile products compounded under procedures other than in Chapter 1206 [Sterile Drug Products for Home Use] of the United States Pharmacopeia (USP)"

When the 2000-2005 SCC was constituted in Jun 2000, we expected to merely update <1206> to continue as an informational chapter. Two months later we had to radically revise <1206> to an enforceable general chapter numbered less than 1000, and; thus, forestall stricter FDA regulations.

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<797> Raison d'être (cont'd)

Low compliance found in 2002 with Am. Soc. Hospital/Health-System Pharmacists, ASHP, June 2000 voluntary sterile compounding guidelines.

- *Am J Health-Syst Pharm.* 2003; 60: 2567-76

By fall 2002, after several 1990-2002 patient deaths and injuries from unsterile preparations, FDA was considering cGMPs-like regulation, including a DSHEA 1994-like warning label:*

- "This preparation compounded by your pharmacy has not been evaluated for safety and effectiveness by the FDA."
- Clinical correlate: "This BP reading by your pharmacist has not been evaluated for accuracy and competency by your physician."

* Dr. Loyd V. Allen, Jr. and I heard this directly from two top CDER lawyers.

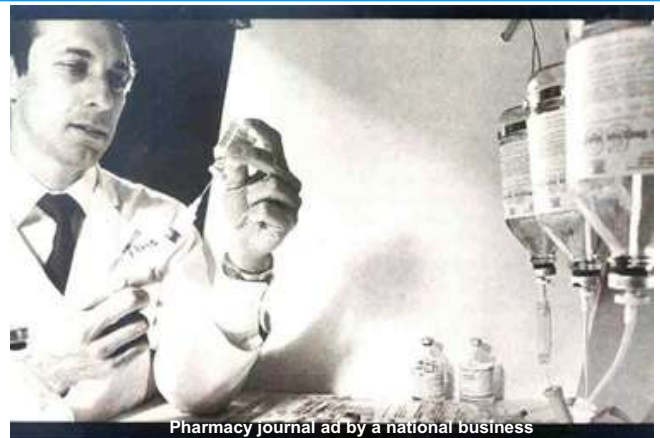
1970's practice was easy to teach and dangerous to patients



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circa 1990 claimed "state of the art"

(ASHP produced the first voluntary national guidelines
Am J Hosp Pharm. 1992; 49:407-17)



Pharmacy journal ad by a national business

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Low-Risk Level with ≤ 12 -hr BUD
When hood is ISO class 5 in worse than ISO class 7 room



post-2004 photo

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<797> compliant ISO class 8 ante area



2008 photo

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Stellar <797> compliant facility



2008 photo

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Joe D. said it best in 2003
 (Countering and anticipating pharmacist resistance)

After USP announced in its Jul-Aug 2003 *Pharmacopeial Forum* that <797> would become official Jan. 1, 2004.

“This [<797>] is all about patient safety. Let’s not forget what the purpose of all this is: to protect patients from microbially contaminated preparations ... make sure those preparations are compounded accurately and appropriately”

Joe Deffenbaugh, Director of Public Health and Quality
 American Society of Health-System Pharmacists (ASHP)
Am J Health-Syst Pharm 2003; 60:1814

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2000-2010 USP SCC Expert Volunteers

- ◆ Dr. Sam Augustine
- ◆ Dr. Mary Baker
- ◆ Dr. Gail Brazeau
- ◆ Dr. Jim Cooper
- ◆ Dr. David Driscoll
- ◆ Dr. Don Filibeck
- ◆ Mr. Larry Griffin
- ◆ Mr. Ken Hughes
- ◆ Mr. Eric Kastango
- ◆ Mr. Keith St. John
- ◆ Dr. Laura Thoma
- ◆ Mr. Larry Trissel
- ◆ Mr. Jim Wagner

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<797> Is Not Just About Sterility

Very concerned with correct identities and amounts of ingredients, e.g.,

- ◆ Death of baby in 2006 from sterile 1000X zinc in TPN
- ◆ Death of baby after year 2001 from sterile IV CaHPO₄ precipitate (*DWN* consulted)
- ◆ Death of 2 yr old girl in 2006 from sterile 23.4% instead of 0.9% NaCl injection
- ◆ Deaths of 3 patients in Portland, OR and Yakima, WA in 2007 from sterile 8X too strong colchicine injection after weighing error at a Texas compounding pharmacy
- ◆ Deaths from mix-ups of sterile heparin and insulin

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Featured 2008 Revisions

- ◆ **Avoid/Minimize Contact Contamination** (vs airborne emphasis in original 2004 chapter):
 - Personnel cleansing and garbing – Appendix III
 - Personnel training – Appendix IV
 - Surfaces and gloves disinfection
 - Gloves and ISO class 5 surfaces sampling
- ◆ **Immediate-Use CSPs**
 - few personnel and no environmental standards
- ◆ **Hazardous Drugs** (antineoplastics)
 - personnel protection
 - separate storage
 - no room-to-room drift

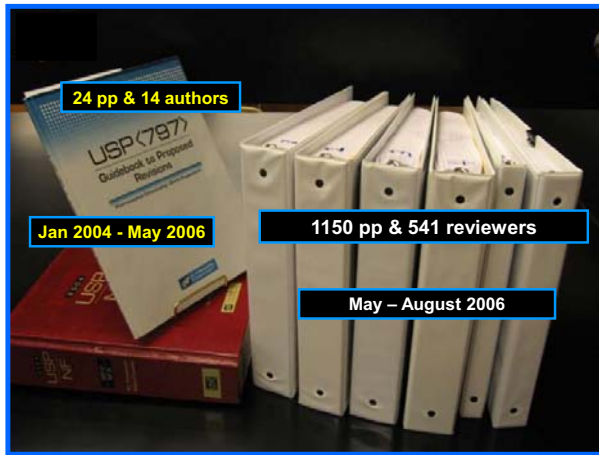
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Synopsis of 2008 First Revision (current <797>)

- ◆ May 2004-Aug 2005: 4 public workshops in MD, SC, and CA; total attendance 600 – predominantly hospital and home infusion pharmacists
- ◆ May-Aug. 2006: public comment period for In-Process (proposed) Revision posted **free** at link on <http://www.usp.org/>
 - Results: see next slide
 - SCC Response : 2-hour conference calls monthly Sep 2006-Feb 2007; biweekly Mar-Nov 2007

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Manuscript Reviewers' Comments



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New 2008 standards to reduce contact contamination sources

- ◆ Hand hygiene: waterless alcohol-based “surgical” scrub with persistent activity (e.g., Avagard™ with 61% ethanol and 1% chlorhexidine gluconate)
- ◆ Sterile gloves to minimize initial bioburden
- ◆ Wipe ampuls, swab stoppers, re-disinfect gloves with sterile IPA (70% v/v isopropyl alcohol)
- ◆ Honest, SCC knows that sterile gloves do not remain sterile, and sterile IPA does not sterilize
- ◆ Do NOT misuse single dose as multiple dose containers

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<797> Personnel Garb and Gloves



2005-2010 SCC member
Eric Kastango

- Hair net
- Beard cover and face mask
- Gown (low shedding)
- Sterile Gloves
- Shoe covers

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Personnel Performance Emphasis

“The new chapter [i.e., the first official <797> revision announced by USP on Nov 27, 2007 to be official on Jun 1, 2008] places much more emphasis on the individual training and evaluation of those who compound sterile preparations. From APIC's* view, the link of performance measures with education and training is welcome ... environmental sampling must occur as part of a comprehensive quality management.”

* Association for Professionals in Infection Control and Epidemiology. February 27, 2008.

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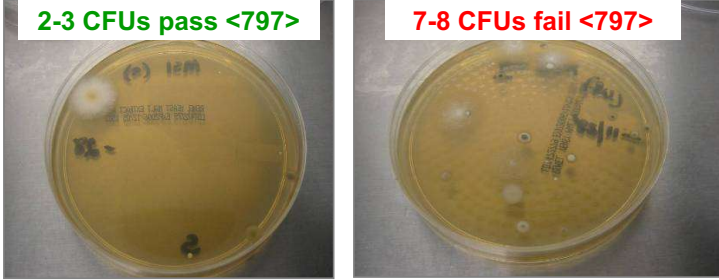
Air Sampling for Viable Microorganisms (same air source at the same time)

Gravimetric Settling
x 4 hours

2-3 CFUs pass <797>

1000L (1m³) Active Impaction
x 5-20 minutes

7-8 CFUs fail <797>



Courtesy of MSI, Inc. Houston, TX (www.microbiologyspecialists.com)

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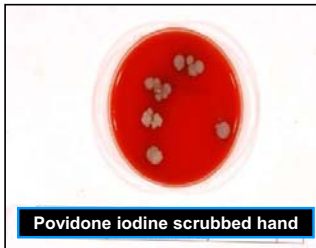
Don't expect a mask to block this!
<797> prohibits compounding by persons with URIs



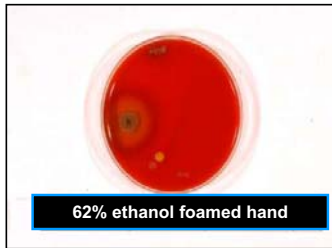
Photo courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy,
Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.

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Initial hand hygiene is essential
(because gloves can imperceptibly puncture and tear)



Povidone iodine scrubbed hand



62% ethanol foamed hand

Blood agar cultures courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy,
Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.

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Even non-sterile IPA reduces glove bioburden



Sterile glove at 1 hr; no IPA

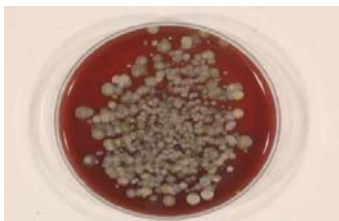


Sterile glove at 1 hr; one IPA spray

Blood agar cultures courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy,
Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.

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Personnel may dislike hair nets and not wearing head jewelry and flaking makeup,
but unknowing patients love it!



uncovered hair – head shake

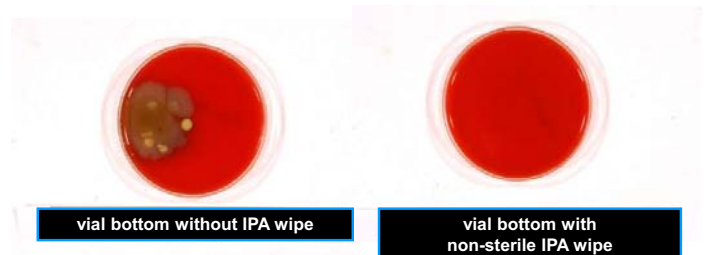


covered hair at 1 hr – head shake

Blood agar cultures courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy,
Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.

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Un-entered vials are only sterile inside



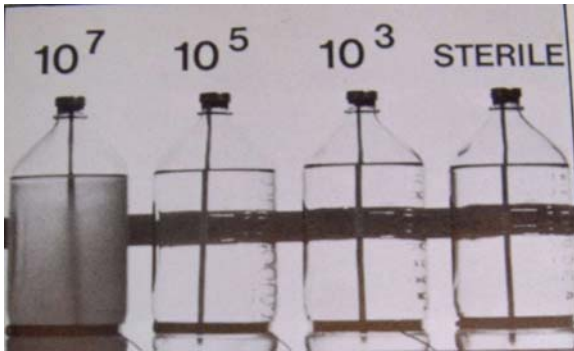
vial bottom without IPA wipe

vial bottom with non-sterile IPA wipe

Blood agar cultures courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy,
Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.

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Breathed, coughed, sneezed, and shed on;
and touched CSPs can look STERILE
as do 10^5 and 10^3 bacteria per mL



Exponential Bacteria per mL in 1L bottles

Millipore Corp. *Hospital Pharmacy Filtration Guide*. (Cat. No. MP801) . Bedford, MA; 1980:3

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<797> “Firsts” for USP (est. 1820)

- ◆ Enforceable public standards of practice
- ◆ Most ever public comments received and addressed to revise a chapter or monograph
- ◆ Free public access to text of and email link for comments on an In-Process (proposed) revision of a USP chapter or monograph
- ◆ Creation and free posting of 130 (May 2010) and growing FAQs to interpret and apply standards in a chapter

• <http://www.usp.org/audiences/pharmacist/797FAQs.html>

Int J Pharm Comp (IJPC) papers recommended
for <797> history, rationale, and application

History and Rationale

- ◆ Newton DW, Trissel LA. 2004; 8:251-263
- ◆ Okeke CC, Newton DW, Kastango ES; Allen LV, Jr. 2008; 12:530-536*

*In which Table 1 means Table 1 in *IJPC*. 2008; 12:136-144, and Figure 1 named in line 3 of the left column on page 532 was inadvertently omitted ; it is the photo on slide 15 in this set.

Application and Interpretation

- ◆ Okeke CC and Allen LV, Jr. Articles on particular <797> sections in multiple 2008, 2009, and 2010 issues

Public and Personal <797> Legacy

- ◆ <797> is endorsed or enforced wholly or partly by:

- ACPE (Standards 2007, Appendix B, page vi)
- AMA (policy H-120.945, summer 2006)
- APIC • FDA • Joint Commission • PCAB Standard 3.30
- Several U.S. state boards of pharmacy and medicine
- Individual U.S. and foreign institutions and facilities

- ◆ “The road to success is always under construction” and the USP is always under revision; so, expect more <797> refinements, but not major change\$.

- ◆ I treasure sharing the uncommon dedication of 13 colleagues and 3 USP staff liaisons from 2000-2010 whose common purpose to protect patients treated with drug and nutrient CSPs benefitted from considering the comments of hundreds of individual and dozens of organizational <797> stakeholders.

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Dr. Gina Peacock assessing a P3 student
in PHAR 713 at Shenandoah University



Apr 2010

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Questions for Program Objective 1

1. USP <797> places the greatest emphasis on which area:
 - a. Principles and applications of sterilization methods
 - b. Personnel cleansing, garbing, and manipulative skills
 - c. Assignment of appropriate beyond-use dates
 - d. Environmental monitoring and facilities cleaning
2. Which motivated the 2000-2003 creation of USP <797>:
 - I. Low ASHP member compliance with voluntary ASHP guidelines
 - II. FDA considering adoption of regulations with industry-like rigor
 - III. Shortages of several commercially manufactured drug injections
 - a. I only
 - b. III only
 - c. I and II
 - d. II and III
 - e. I, II, and III

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