

4

EXHIBIT 4

December 2, 2002

Revisions Committee
c/o John Cronin, CPhA
1112 "I" Street, Suite 300
Sacramento, CA 95814

Re: California Board of Pharmacy December 5, 2002 Proposal on CCR 1751 et seq.

John and Committee:

The International Academy of Compounding Pharmacists (IACP) supports the comments issued by the committee of compounding pharmacists reviewing the California Board's proposed sterile regulations ("the committee"). Of these comments, IACP believes that the committee's modifications to Title 16 CCR 1751.3 (a) "Record keeping Requirements" are especially imperative. IACP supports the revisions and changes to Section 1751.3. IACP supports the rationale that "most of the records addressed by this section are either kept as part of the patient profile, are not available to the [community] pharmacist, or are not relevant to the use of a product administered in a prescriber's office. They should be required only in institutional settings."

While IACP supports the committee's comments, we wish to address a number of additional concerns related to these regulations. IACP's primary concerns include the regulations regarding extensive end-product testing, expiration dates, and sterile gloves. However, a number of clarifications and lesser modifications are additionally outlined below. We ask that you consider the inclusion of these points in your revisions, which will be presented to the California Board of Pharmacy during their December 5, 2002 meeting.

IACP's concerns include:

Title 16 CCR 1751. (a) (5) "Cardboard boxes"

IACP agrees that cardboard boxes should not be allowed in cleanrooms or the "designated area for the preparation of sterile injectable products." However, we see no reason to prohibit the storage of properly packaged chemicals or equipment in cardboard boxes prior to their use. IACP asks that the words "may not be stored in corrugated cardboard boxes and" be removed from Section 1751. (a) (5).

Title 16 CCR 1751.3 (b) (2) "Refrigerator and freezer temperatures "

Section 1751.3 (b) (2) requires pharmacies to keep a log of refrigerator and freezer temperatures. This requirement is overly burdensome to pharmacists and contributes little to the purpose of increasing quality control. This requirement should be removed.

Title 16 CCR 1751.3 (b) (6) “...Records of End-Product Evaluation Results”

Section 1751.3 should not be interpreted to require end-product testing for every product a pharmacy prepares. Testing for sterility, potency, and endotoxin level at an independent laboratory typically adds \$200-\$300 cost per compounded prescription. The cost of this testing would be prohibitive to both pharmacy and patient. IACP recommends the revision of this section to read, “Preparation records including the master worksheet, the approved preparation worksheet, and results of sampling for end-product sterility and endotoxin level.”

Title 16 CCR 1751.4 (b) (3) “...Covered with a Sterile Glove”

Sterile gloves are not routinely used in aseptic compounding by hospital, chain, or community pharmacies. Additionally, experts in sterile product preparation do not recommend use of sterile gloves. Sterile training, policies, and procedures should indicate that gloves should not come into contact with the sterile product. Gloves should not have direct contact with the drug product. Thus, the initial sterility of the gloves should not affect the product integrity and this regulation should be expendable. Further, sterile gloves cost three times more than non-sterile gloves while making no significant contribution to finished product quality. The word sterile should be removed from Section 1751.4 (b) (3).

Title 16 CCR 1751.7 (a) (3) “Exhaustive end product testing must be documented prior to the release of product from quarantine...”

IACP agrees with the committee’s elimination of the reference to manufacturing in this section. However, IACP requests a much stronger argument against the mandate of “extensive end-product testing” for compounded sterile injectable products.

Mandating “extensive end-product testing” would be financially devastating to pharmacies and patients and would undermine the purpose of this regulation. Testing for sterility, potency, and endotoxin level at an independent laboratory typically adds \$200-\$300 per compounded prescription. In order to avoid financial devastation of sterile compounding operations, pharmacies must increase revenues to balance the rising costs associated with complying with these regulations. However, increased revenues are unlikely. In an increasingly competitive and global market, networking with out-of-state or international pharmacies to obtain prescription drug products at lower costs is an increasing consumer practice. Thus, in response to stringent compliance costs that will likely be distributed to consumers, California patients are likely to employ outside resources to more economically fill sterile prescriptions. The standards would decrease public health and safety as prohibitive prices encourage consumers to resource external, and potentially non-regulated, sources for prescription drugs.

The process validation techniques, outlined in these regulations should satisfy product validation requirements. Referencing Remington’s Pharmaceutical Sciences, IACP believes that process validation is a more effective quality indicator than end-product testing. If desired, an end-product testing program, conducted according to a formal sampling plan, may supplement the

process validation techniques. However, process validation should be maintained as the primary method of quality assurance. IACP recommends the following language, adapted from ASHP regulations, describing end-product testing.

Process validation should be supplemented with a program of end-product sterility testing, according to a formal sampling plan. Written policies and procedures should specify methods of testing. Policies and procedures should include acceptance criteria for the sampling and testing. Products not meeting all specifications should be rejected and discarded. There should be a mechanism for recalling all products of a specific batch if end-product testing procedures yield unacceptable results.

In addition, the statement “testing must be documented prior to the release of the product from quarantine” is extremely problematic. End-product testing can require two-weeks or longer to complete. Several sterile products must be compounded by pharmacists because their shelf life is too short to allow for transport from a manufacturer. Requiring end-product testing results prior to the release of these products would entirely preclude their use. In addition, there are times when immediate patient need for a drug product exceeds the risk of product corruption. The release of a drug product from quarantine should always be subject to a pharmacist’s judgment. The pharmacist should consider the patient risk versus the potential risk in his/her decision. Pharmacies should also have a mechanism for recalling dispensed products if testing yields unacceptable results.

IACP recommends the removal of Section 1751.7 (a) (3) from California regulations. Section 1751.7, “Quality Assurance,” sufficiently addresses process validation (1751.7 (b) [and (c) in CPHA, et al revisions]) and appropriate end-product testing (1751.7 (a) (2)).

Title 16 CCR 1751.7 (a) (6) “...Chosen Expiration Dates”

The phrase “expiration date” should not be used in reference to compounded drug products or components. “Expiration date” is a term that should be used exclusively in reference to manufactured drug products, as dating is determined based on differing methodologies and criteria for manufactured and compounded therapies. “Beyond-use date” is the appropriate reference for a compounded medication¹. Beyond-use dates should be assigned based on data presented in peer-reviewed literature, appropriate testing, pharmacopoeial standards, or the pharmacists’ education and experience.

¹ “The beyond-use date is a defined period of time that starts from the original date the parenteral admixture was made until it is deemed unacceptable for clinical use, after which the compounded sterile product should not be used. . . . The beyond-use dates may be assigned based on criteria different from those applied to assigning the expiration dates to manufactured drug products. For example, a higher concentration of drug may be described; different diluents or container may be necessary; or the patient may require the [Compounded Sterile Product (CSP)] for longer periods of time. In these instances, a pharmacist must be consulted to ascertain a reasonable extension of the product’s beyond-use life outside of the approved package insert. In assigning a beyond use date for a CSP, pharmacists should use their pharmaceutical education and experience.” (USP Chapter 797, “Pharmaceutical Compounding – Sterile Preparations”)

Title 16 CCR 1751.8 (b) (3) (G) (CPhA group Section 1751.1) “...Controlled Area”

This section repeatedly uses the phrase “controlled area.” “Controlled area” is not defined in these standards. The word “cleanroom” or the phrase “designated area for compounding sterile injectable products” should be substituted for the two occurrences of this phrase in Title 16 CCR 1751.8.

Title 16 CCR 1751.8 (b) (3) (L) (CPhA group Section 1751.1) “End-Product Evaluation and Testing”

Section 1751.8 (b) (3) (L) should not be interpreted to require end-product testing for every product a pharmacy prepares. Testing for sterility, potency, and endotoxin level at an independent laboratory typically adds \$200-\$300 cost per compounded prescription. The cost of this testing would be prohibitive to both pharmacy and patient. IACP recommends the revision of this section to read, “Preparation records including the master worksheet, the approved preparation worksheet, and results of sampling for end-product sterility and endotoxin level.”

Title 16 CCR 1751.9 (a) and (b) “Parenteral Therapy”

Title 16 CCR 1751 now addresses “sterile injectable compounding.” Section 1751.9 should be updated accordingly.

IACP thanks the committee for consideration of these comments. If we can be of further assistance, or if you have any questions, please do not hesitate to contact me or Jennifer Brashares, IACP’s Regulatory Affairs Coordinator, at (800) 927-4227.

Sincerely,

L.D. King
Executive Director

cc: Jennifer Brashares, Regulatory Affairs Coordinator