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EXHIBIT 3

January 31, 2003

Missouri State Board of Pharmacy
c/o Kevin Kinkade, Executive Director
P.O. Box 625
Jefferson City, MO 65102

Re: Proposed Rule 4 CSR 220-2.200 Sterile Pharmaceuticals

Members of the Missouri Board of Pharmacy:

The International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to comment on the Missouri Board of Pharmacy's proposed rule "4 CSR 220-2.200 Sterile Pharmaceuticals." IACP is an international, non-profit association representing pharmaceutical compounding. IACP represents pharmacists who prepare customized medications according to a physician's specifications to meet unique patient needs. IACP's mission includes increasing awareness of the importance of compounding by providing accurate information on the benefits of compounding and providing assistance to pharmacists in improving their compounding activities. In this capacity, IACP wishes to address a number of concerns with these regulations. IACP submits these comments on behalf of its Missouri members, who will be directly impacted by these regulations, and additionally their patients, who benefit from compounded medications.

Initially, IACP believes that the Missouri Board of Pharmacy's entire approach to the regulation of sterile pharmaceutical compounding is fundamentally flawed in that it places primary emphasis and dependence on end-product testing. As will be demonstrated throughout these comments, ~~over-reliance on product testing is inefficient, extremely expensive,~~ and only partially effective for assuring product quality. With millions of dollars at stake for both pharmacies and patients, IACP recommends that the Missouri Board of Pharmacy consider an alternative approach to the regulation of sterile products – the implementation of systematic process controls.¹ Such an approach will be more efficient, economical, and effective for ensuring product quality and patient safety.

Pharmaceutical experts contend that the integration of systematic process controls in a compounding pharmacy is the ideal means of assuring product quality. "Systematic process control' is defined as validated policies, procedures, and processes that are used to consistently produce products of the highest quality."^{1b} Systematic process controls include:

¹ For a comprehensive discussion of the merits and implementation of systematic process controls for sterile pharmacy compounding operations, please reference the following articles:

- ^a Kastango ES, Douglass K. Improving the Management, Operations, and Cost Effectiveness of Sterile-Product Compounding. *International Journal of Pharmaceutical Compounding*. 1999; 3: 252-258.
- ^b Kastango ES, Douglass K. Quality Assurance for Sterile Products. *International Journal of Pharmaceutical Compounding*. 2001; 5: 246-253.

We have included a copy of these articles for your reference.

- Compliance with operating policies, procedures and processes and the documentation generated from their execution;
- Initial and ongoing employee education using didactic, practicum and on-the-job training strategies;
- Personnel controls such as proper handwashing, gowning and gloving procedures and successful aseptic technique validation; and
- Air surface sampling tests of critical work areas.¹⁰

Monitoring and evaluation of data generated from these operations can provide a comprehensive picture of product quality and facility aptitude for sterile compounding operations.

Endorsement of systematic process controls would involve a greater emphasis on activities such as personnel and process validation testing through media fills, equipment validation, and environmental quality sampling. If processes are executed accurately, the Missouri Board of Pharmacy and the pharmacy preparing sterile products should have a high degree of confidence in the final product quality. As outlined in *Remington's Pharmaceutical Sciences*,² there is a much greater degree of uncertainty and inaccuracy involved in end-product testing than in verifying accurate execution of processes.

In addition, "systematic process control relies on prospective data monitoring and collection versus retrospective analysis such as end-product testing. The results of end-product testing (sterility or quantitative analysis) are generally not known prior to product release for patient use."^{1a} Further, systematic process controls allow for greater diagnostic capabilities in the event an error does occur in a pharmacy operation. Process controls enable the pharmacy to quickly diagnose and correct potential problems in sterile compounding operations.

Finally, ~~endorsement~~ of systematic process controls will greatly reduce costs to Missouri pharmacies and patients. According to process control methodology, variables such as sterility, pyrogenicity, and potency are dependent on proper execution of validated processes. Given validated processes, product quality indicators such as sterility, pyrogenicity, and potency should be intrinsic to the product. There would be no need to quantitatively test every batch or product for accuracy. Quantitative end-product testing would instead be performed on a sampling basis, as a double-checking mechanism. This would greatly reduce the amount of capital a pharmacy would need to invest in testing. Likewise, the costs of sampling distributed to patients would be greatly reduced and could be equally distributed among the pharmacy's patients.

Overall, process validation is much more efficient, economical, and indicative of product quality than end-product testing. The Missouri Board of Pharmacy should consider adopting this regulatory strategy for governing state sterile compounding operations.

² Osol A (ed). *Remington's: Pharmaceutical Sciences*. Easton, PA: Mack Publishing Company. 1980' 16: 1400-1402.

Specific Issues

IACP has several additional concerns with specific regulations that the Missouri Board of Pharmacy has promulgated to govern the compounding of sterile pharmaceuticals.

4 CSR 220-2.200 (1) "Definitions."

IACP maintains a number of concerns with the definitions outlined in Part (1).

Initially, IACP believes that the Missouri Board of Pharmacy's definition of "Compounding" provided in Section (H) is too broad. As written, the compounding definition would include the reconstitution or manipulation of FDA-approved, commercial products. Most applicable federal and state definitions of compounding do not include reconstitution, manipulation, or sterile admixture according to FDA-approved labeling. In fact, the Congressionally-endorsed definition of compounding provided by the Food and Drug Administration Modernization Act of 1997 (FDAMA), which added Section 503A to the Federal Food Drug and Cosmetic Act (FDCA),³ specifically exempts reconstitution, et al. of commercial products from consideration as elements of compounding pharmacy practice. "...The term 'compounding' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling." Inclusion of practices (such as admixture, reconstitution, and other manipulations of commercial products) that are consistent with FDA-approved labeling in the definition of compounding can introduce considerable confusion into traditional pharmacy practices. For example, expiration dating of products becomes extremely complicated, as an expiration date is the appropriate reference for FDA-approved products and a beyond-use date is the appropriate reference for compounded products. As stated, the Missouri definition of compounding conflates two distinct categories of products. Admixture, reconstitution, or other manipulations of commercial products according to FDA-approved labeling should not be included in the definition of compounding. The Missouri Board should clarify their definition of compounding to exclude admixture, reconstitution and manipulation of commercial products.

Further, the phrase "expiration date and time shall be assigned..." in the definition of "Expiration Date" (Section (N)) implies a Board endorsement of assigning expiration dates to compounded drug products. However, the term "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 medication.⁴ The Missouri Board of

³ FDAMA Section 503A was struck down in *Western States v. Tommy Thompson* because advertising restrictions in the regulations were found to be unconstitutional. This decision does not jeopardize the significance of Congressional language clearly distinguishing between compounding and reconstitution, et al. according to FDA-approved labeling.

⁴ "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

Pharmacy should recognize this distinction in the definitions and throughout the proposed regulations. In addition, IACP recommends adding a definition of "beyond-use date" to Part (1) for reference with compounded products. (See USP Chapter <795> for additional information on beyond-use dating.)

4 CSR 220-2.200 (7) Aseptic Technique and Product Preparation

Additionally, IACP maintains a number of concerns with the requirements outlined in Part (7) "Aseptic Technique and Product Preparation."

Initially, IACP is concerned that the Section (C) "Risk Level 3" statement, "Nonsterile components must meet USP standards for identity, purity and endotoxin levels..." would require testing of bulk active pharmaceutical ingredients. In fact, the definition of Quality Control,⁵ as well as process validation⁶ and record keeping⁷ requirements, seem to confirm testing requirements (identity, purity, non-pyrogenicity and sterility) for ingredients and components of sterile products. IACP has several concerns with component testing requirements.

To begin, pharmacies are generally not equipped with the equipment or skill necessary to test bulk drugs for identity, purity, non-pyrogenicity, or sterility. IACP is aware that the Missouri Board of Pharmacy discussed in meetings the use of Certificates of Analysis to satisfy this requirement. However, Certificates of Analysis often do not carry information on pyrogen level or sterility of products, especially for non-sterile components. The inability of a Certificate of Analysis to satisfy this requirement would force in-pharmacy or laboratory testing of all bulk active pharmaceutical ingredients and excipients used in sterile compounding. Requiring testing of active pharmaceutical ingredients or excipients would be extremely problematic. At the outset, the cost of this testing would be prohibitive. Like end-product testing, in-house or laboratory testing for sterility, potency, and endotoxin level could cost as much as \$600 per component. Component testing would immensely increase patient prescription costs. Additionally, requiring this testing would hinder patient access to important therapies, as valid test results require time to obtain – sometimes in excess of a week.

Furthermore, requiring testing of ingredients or components would result in excessive repetition and waste of funds. As written, the Missouri regulations require end-product testing of all products prepared from non-sterile components. End-product testing results would verify

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")

⁵ Part (1) "Definitions" Section (T)

⁶ Part (8) "Process Validation" Section (C) "Risk Level 3"

⁷ Part (9) "Record Keeping" Section (C) "Risk Level 3" (5)

component quality, as the final product could not satisfy end-product tests without use of quality components. In addition, in-pharmacy or independent laboratory end-product testing for sterility, potency, and endotoxin level can add more than \$800⁸ per compounded prescription. Testing of components would attach additional costs to every compounded prescription. If testing were required at the beginning and end of all sterile processes, the combined costs of testing could increase to more than \$1,000 per compounded product, with no added quality benefit. These costs would render current and appropriate pharmaceutical care cost prohibitive, as patients will not pay \$1,000 for a vial of medication.

For the reasons presented above, the United States Pharmacopeia (USP) and other standard-setting organizations do not require pharmacies to test bulk active pharmaceutical ingredients or excipients. Pharmacists should be able to satisfy any component validation requirements through use of their professional judgment in selecting reputable sources of supply and through inspection of a Certificate of Analysis, when applicable. Suppliers are held accountable for quality of active pharmaceutical ingredients through regulation according to Good Manufacturing Practices (GMPs), as well as registration and inspection by FDA and applicable State Departments of Health. The problematic statements identified previously should be revised to eliminate reference to component testing for ingredients used in sterile product preparation.

IACP maintains a second major concern with the Section (C) statement, "Nonsterile components must meet USP standards for identity, purity and endotoxin levels..." While IACP agrees that it is generally better for pharmacists to use pharmacopoeial grade ingredients, in many cases there are no monographs outlining appropriate standards. In cases where there is not an official standard for an ingredient, the pharmacist must rely on his/her professional judgment along with an assessment of the Certificate of Analysis to evaluate the quality of the ingredient. IACP recommends revision of this regulation to allow pharmacists to satisfy the "USP standards" requirement through receiving from their immediate supplier documentation accompanying the drug, such as a Certificate of Analysis.

Further, there are two primary categories of bulk drugs: active ingredient and excipients. References to "components" and "ingredients" throughout Section (C) could be interpreted to require testing of both active pharmaceutical ingredients and excipients. Component validation requirements should be limited to active pharmaceutical ingredients, as excipients often are not the subject of official monographs and validated testing methods. The Missouri Board of

⁸ The Missouri Board of Pharmacy estimates that end-product testing on every batch would cost approximately \$805. IACP believes that this estimate may be inaccurate. The Missouri Board, in its Private Entity Cost Worksheet (see Page 17, January 2003 Missouri Register), estimates that pyrogenicity testing would cost \$30 per batch. However, the Missouri Board also requires, in its end-product evaluation requirements, that pyrogenicity tests comply with USP methods. The referenced \$30 in-house endotoxin testing kits do not satisfy the stringent USP standards. To comply with USP methods for endotoxin testing, pharmacies would be forced to outsource endotoxin testing. Endotoxin testing at analytical laboratories costs approximately \$150 per sample. Thus, end-product testing costs on every batch of sterile product prepared could increase to as much as \$925.

Pharmacy should replace all references to "components" with the phrase "active pharmaceutical ingredient."

4 CSR 220-2.200 (9) Record Keeping

The phrase, "Ingredient validation," in Section (C) "Risk Level 3" Number (5) is not defined. This section requires pharmacists to keep records of "ingredient validation." However, Missouri regulations have not clearly defined what processes would satisfy this requirement. As outlined in IACP's comments on Section (7), ingredient validation should not include formal testing requirements. Instead, evaluation of product characteristics such as particle size and shape, color, homogeneity, clarity, container weight variation, etc. using appropriate references and standards, such as a Certificate of Analysis, could provide sufficient "ingredient validation" for components or ingredients used in compounding. Regardless, the term "ingredient validation," as referenced in Section (C) Number (5), is inappropriate and needs to be modified or removed.

4 CSR 220-2.200 (11) Expiration Dating

As previously discussed, the appropriate reference for a compounded medication is "beyond-use date." The Missouri Board of Pharmacy needs to recognize this distinction throughout this section and the proposed regulations.⁹

In addition, IACP believes that the "laboratory testing" required in Section (C) "Risk Level 3" is excessive. IACP believes that this requirement places an unnecessary and unduly restrictive burden on pharmacists. Initially, a defining characteristic of pharmaceutical compounding practice is the ability to create a variety of formulations, dosages, and dosage forms to meet unique patient needs. Thus, there is tremendous variance in the types of drug products produced by compounded pharmacists. On the other hand, manufacturers, to ensure a return on their investment, produce only a narrow range of chemical forms, dosage forms, strengths, flavors, and packaging. The narrow scope of manufacturing allows manufacturers to perform extensive testing on their products. However, the nature and scope of compounding makes exhaustive testing prohibitive. It is neither feasible nor prudent to test every formulation, every dosage, and every dosage form that a pharmacy compounds. Performing stability testing is beyond the scope of traditional pharmacy practice and would require stability studies by independent analytical laboratories. Testing costs for stability studies at independent laboratories require a minimum investment of approximately \$10,000 per compounded formulation. Thus, the cost of this testing would be prohibitive to both pharmacies and patients (as testing costs would likely be distributed to consumers). Further, requiring stability testing would hinder patient access to important therapies, as stability testing usually requires a minimum of one to three months to perform. Pharmacists do not usually receive prior notice on prescribed therapies and certainly are not given months of advanced notice to allow for extensive stability testing on formulations. Thus, stability testing, as mandated, would restrict patient access to crucial therapies and customized medications.

⁹ Correction Needed: Part (10) "Labeling" Section (A) "Risk Level 1" (1) "Expiration date"

For this reason, pharmacopocias set standards for applying beyond-use dates to compounded medications. As indicated previously in Footnote 4, beyond-use dates should be assigned based on data presented in peer-reviewed literature, appropriate testing, pharmacopoeial standards, or the pharmacists' education and experience. In the absence of stability information from these sources, pharmacists should be able to reference publications such as *Trissel's Stability of Compounded Formulations*¹⁰ and apply their professional education, experience, and judgment to determine appropriate stability parameters for compounded drug products. Pharmacists can also reference compounding standards, such as USP Chapter 795, which provide guidelines for establishing appropriate stability parameters on products based on formulation. Testing is beyond the scope of compounding pharmacy practice.

4 CSR 220-2.200 (12) End-Product Evaluation

IACP maintains a number of concerns with the standards outlined in Part (12) Section (C) "Risk Level 3."

Initially, IACP maintains great concern with the requirement in Section (C) "Risk Level 3" that "each sterile preparation or batch must be tested for sterility, pyrogenicity, and potency." Mandating end-product testing for every Risk Level 3 product would be financially devastating to pharmacies. The cost would additionally be prohibitive to patients. Testing for sterility, potency, and endotoxin level at an independent laboratory could exceed \$800¹¹ per batch, according to Board estimates. In-house testing reduces costs only minimally. In order to avoid financial devastation of sterile compounding operations, pharmacies must increase revenues to balance costs associated with complying with these regulations. However, increased revenues are unlikely and, thus, costs must be distributed to patients. In an increasingly competitive and global market, consumers are networking with out-of-state or international pharmacies to obtain prescription drug products at lower costs. Missouri patients are no different. Missouri patients are likely to employ outside resources to more economically fill sterile prescriptions in response to the stringent compliance costs that will be distributed to consumers. Products compounded in other localities not subject to Missouri standards will saturate the Missouri market, nullifying the intended outcome of these regulations. Accordingly, the Missouri Board of Pharmacy will invalidate its goal of increasing patient health and safety as prohibitive prices drive consumers to resource external sources for prescription drugs.

Instead, IACP strongly endorses process and personnel validation as excellent indicators of sterile product quality. Following logic provided in *Remington's Pharmaceutical Sciences*,² experts believe that process and personnel validation are more effective quality indicators than end-product testing. Process and personnel validation should be the foundation of quality control for sterile products. Missouri has already outlined appropriate process validation procedures within the proposed sterile regulations.

¹⁰ Trissel, L.A. *Trissel's Stability of Compounded Formulations*. Washington, DC: American Pharmaceutical Association; 2000.

¹¹ \$925, as outlined in Footnote 8.

In addition to process validation requirements, a sampling program for end-product sterility, pyrogenicity, and potency can be instructive. Missouri has already recognized the value of a sampling program for sterility testing in Section (C) "Risk Level 3" Number (1) "Sterility Testing." However, for the reasons outlined above, the Board of Pharmacy should adhere to a sampling program for all sterility, endotoxin, and potency testing. Several other standard setting organizations, such as the American Society of Health-System Pharmacists (ASHP) endorse end-product sampling programs, as outlined in a pharmacy's policy and procedure manual.

The Missouri Board should continue to endorse process validation while end-product testing should not be required as rigorously. A sampling program reinforces process and personnel validation, however minimizes the profligate investments required to test every sterile compound. Likewise, frequency of end-product testing samples should be relegated to a pharmacist's professional judgment (based on scale of operations, types of manipulations performed, batch size, frequency of compounding the particular product, the compounding risk level of the product, and the potential risk to the patient) and outlined in the pharmacy's policy and procedure manual.

IACP maintains additional concern that in existing Section (C) regulations the Board has allowed sampling for sterility but mandated endotoxin testing "for each sterile product prepared from non-sterile drug components...." Lack of sterility is more critical to patient health than the presence of an endotoxin, which may result only in a temporary fever. Thus, sterility testing should be given more emphasis in regulations than endotoxin testing. The proposed regulations place far too much emphasis on endotoxin testing, relative to sterility testing. Additionally, potency may be effectively verified through process controls, such as checking printed data from balances and adherence to written formulations. Potency testing of compounds may not be as critical as testing for sterility and endotoxins. Likewise, as outlined above, all testing should be conducted according to a formal sampling plan.

Moreover, the requirements in Section (C) Number (2) "Pyrogen/Endotoxin Testing" should not apply to every sterile product preparation. Ophthalmic and inhalation solutions are not injected and thus endotoxin testing may not be as critical on these products. The degree of emphasis awarded to specific end-product tests should correlate to the degree of risk applicable to the product prepared. In other words, comprehensive endotoxin testing should not be required when the presence of an endotoxin in a product would pose little or no risk to a patient's health. Determination of testing requirements relative to product risk should be subject to a pharmacist's professional discretion, as outlined in the pharmacy's policies and procedures governing its sampling program for end-product testing.

In addition, requiring USP methods for endotoxin testing for every product would be much too stringent and expensive. The Missouri Board of Pharmacy, in its worksheet describing Private Entity Costs, estimates that pyrogenicity testing per batch would cost pharmacies approximately \$30. However, this \$30 estimate refers to the in-house tests that do not meet these stringent USP Chapter <85> standards. To meet USP <85> standards, pharmacies would be forced to relegate

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all endotoxin testing to independent laboratories at an estimated cost of \$150 per sample.¹² Several in-house endotoxin testing kits are available that may provide pharmacists with appropriate assurance of product quality but may not comply with the extensive requirements of USP <85> governing endotoxin testing. Section (C) Number (2) should be revised to eliminate reference to USP testing standards.

Section (C) further requires that "samples shall be statistically adequate to reasonably ensure that batches are sterile." This requirement is virtually impossible to fulfill. *Remington's Pharmaceutical Sciences*² presents data to demonstrate the inadequacies of 'end product' sterility testing. Experts on sterile product testing state that "the sample size... has a relatively small effect in improving the probability of accepting lots [of product tested]. Even a sample size of 500 [from a 1000 item batch (50%)] would result in erroneously accepting a lot six times out of ten." Thus, "statistically adequate" testing is an impossible standard to achieve. *Remington's* asserts that "the only method for determining sterility with 100% assurance would be to run a total sterility test; i.e. to test every item in the lot." Testing every item is not feasible for any pharmaceutical operation. Therefore, process and personnel validation are considered by experts to be much better indicators of product quality than end-product testing.

Section (C) Number (3) "Potency" Part (D) requires that "the final potency [be] confirmed by instrumental analysis." During the September 2002 meeting of the Missouri Board of Pharmacy, a Board member suggested that refractometers be used for potency evaluation. However, pharmaceutical experts contend that use of a refractometer is an invalid method of assessing potency. This methodology is fundamentally flawed in a number of ways. Variables, such as the presence of multiple ingredients, preservatives, buffers, and other inactive ingredients in a compound or variance in pH and temperature, can render such instruments useless for use in potency evaluation and yield inaccurate results. The instruments are not validated for testing potency of compounds, as this testing is not the intended use of the equipment. The only valid testing methods would involve High-Pressure Liquid Chromatography (HPLC) or Gas Chromatography (GC) or some similar method. "Instrumental analysis" of potency exceeds the scope of traditional pharmacy practice. All validated methods of "instrumental analysis" would require independent laboratory testing or purchase of extremely expensive testing equipment by the pharmacy. All methods would force pharmacy to incur large costs and distribute a large portion of these costs to consumers. Instead of requiring instrumental analysis on all products, pharmacies could include potency testing in their end-product sampling programs. IACP requests that the Missouri Board revise Number (3) Section (D) according to the suggestions outlined above or remove the requirement. Cost estimates for the Board of Pharmacy¹³ should also be revised to eliminate reference to refractometers, as they are not suitable to verify potency.

Further, in light of the Missouri Board's regulatory approach, IACP agrees that the provision for "Emergency Dispensing..." outlined in Section (4) is essential to the continuity of pharmacy

¹² The increased cost of endotoxin testing would affect testing estimates in the Missouri Board's Private Entity Fiscal Note (Page 17, January 2003 Missouri Register). As outlined in Footnote 8, testing costs would increase to \$925 per batch.

¹³ See Public Entity Fiscal Note. Page 14 and 15, January 2003 Missouri Register.

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practice. The emergency dispensing provisions are essential to any regulations that require that "sterile products compounded from non-sterile components must be quarantined pending results of end product testing," as 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. Thus, the emergency dispensing provision in Section (4) is vital to pharmacists' ability to meet patient needs. However, requiring pharmacists to release only the "quantity of product to meet the needs of the patient until all sterility and pyrogenicity tests are known" is overly burdensome. As outlined above, due to stability factors, some products require dispensing of the entire product immediately. Requiring dispensing of a minimal amount would also add time, costs, and confusion for both the patient and the pharmacy. Pharmacies should initially be allowed to dispense the entire product, provided they have a mechanism for recalling dispensed products if testing yields unacceptable results. The recall of a compromised drug would serve the same purpose as dispensing a minimum quantity. USP proposed Chapter <797>, "Pharmacy Compounding - Sterile Preparations," agrees with the recall premise outlined above.

Additional regulations that should be addressed based on the above comments include:

- Part (4) "Storage and Handling" Section (B) "Risk Level 3": The statement, "Finished but untested products must be quarantined under minimal risk for contamination or loss of identity in an identified quarantine area," implies that every batch will be tested. This statement needs to be qualified to allow appropriate storage for products that will not be tested, due to classification in a lower risk category or as a batch or product not sampled.
- Part (7) "Aseptic Technique and Product Preparation" Section (B) "Risk Level 2": The phrase, "final evaluation, and testing," implies that the file maintained on each Risk Level 2 product must contain testing results. However, Section (12) "End Product Evaluation" requires only a final evaluation, not testing, on Risk Level 2 products. The word testing should be removed from Part (7) Section (B) to eliminate the contradiction with Section (12) requirements.
- Part (9) "Record Keeping" (C) "Risk Level 3" (4) "End-product evaluation and testing records": As end-product testing should not be required on every batch or every product, this statement should be clarified, like its predecessors, with the phrase, "if applicable."

4 CSR 220-2.200 (13) Handling Sterile Products Outside the Pharmacy

IACP requests revision of the Part (13) Section (A) "Risk Level 1" requirement that "Sterile products shall be transported... within temperature-controlled delivery containers (as defined by USP standards)." Initially, the word "control," used in pharmacy settings (i.e. controlled release capsules, controlled substances, etc.), communicates a degree of intensity and accuracy in regulation that is overly restrictive when applied to temperature and delivery devices. Further, the cited USP guidelines (presumably, "Packing" from USP proposed Chapter <797>, "Pharmaceutical Compounding - Sterile Preparations") are far too stringent and often beyond the

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scope of traditional pharmacy practice. IACP recommends revision of this Section (A) requirement to state, "Sterile products shall be transported... within appropriate packaging or delivery containers that maintain necessary storage conditions to preserve the quality and integrity of sterile products."

4 CSR 220-2.200 (15) Exemption

The exemption provided in Part (15) of the Missouri Sterile Compounding Regulations is extremely vague. IACP is unclear as to the distinction between "products contained only in a closed or sealed system" (i.e. products exempt in Part (15)) and "products that are sterile throughout the entire compounding process" (referenced in Part (1) "Definitions" Section (Z) "Risk Level 1" and "Risk Level 2"). To maintain sterility throughout the entire compounding process, it is necessary to maintain products within a closed or sealed system. Therefore, Part (15) perhaps exempts all Risk Level 1 and Risk Level 2 compounding from the requirements of these regulations. This exemption needs to be greatly clarified or removed.

4 CSR 220-2.200 Fiscal Note: Private Entity Cost

The costs of implementation for the Missouri Sterile regulations are astronomical. The Missouri Board of Pharmacy estimates that the private entity cost for the year of implementation would be approximately \$5 million and the continuing costs would be \$3 million per year. The Board assigns this burden to Missouri pharmacies without recognizing or assessing the practical impacts of this multi-million dollar burden. Initially, assigning \$3 million of cost per year to sixty-one recognized pharmacies engaged in sterile compounding implies that each pharmacy would incur more than \$50,000 in recurring expenses every year. This could drive most pharmacies in Missouri out of business. If the pharmacies are to stay in business and meet patient needs, the Missouri Board of Pharmacy fails to recognize that all incurred costs in the pharmacies must be distributed to consumers. This basic premise of business management means that the Missouri Board of Pharmacy has relegated a minimum of \$3 million in costs per year to the Missouri public. Consumers will not tolerate this financial burden, especially in the realm of healthcare where rising prescription costs are already a source of social and political contention. If the Missouri sterile compounding regulations are adopted, Missouri would likely become a dumping ground for out-of-state sterile products made in facilities not meeting the stringent Missouri standards. Thus, these regulations, as written, could greatly devalue the Missouri Board's goal of advancing public health and safety.

In addition, IACP is extremely concerned with the uncertainty and potential error inherent to the Missouri Board's private entity cost estimates.¹⁴ The Missouri Board estimates that only fifteen pharmacies will test sterile products. The Board creates this number by projecting "that a total of 61 pharmacies could be affected by this rule. It is further estimated that 25% of these 61 pharmacies, which is equal to 15 pharmacies, are involved in sterile product compounding which

¹⁴ See January 2003 Missouri Register, Page 17, Number 2

includes non-sterile to sterile product compounding."¹⁵ This estimate is developed without justification. The percentage could easily be 50%, 75%, or even 100%. There are no data to justify the estimates. However, the numbers are crucial to the cost estimates presented. If the percentage of pharmacies engaged in Class 3 compounding and testing were to increase to 75% (45 pharmacies), the private entity cost would increase to over \$9 million.¹⁶ If all identified pharmacies engaged in sterile compounding (61 pharmacies) were to perform Class 3 operations, the private entity cost would increase to almost \$13 million.^{17,18}

Further, these costs are based on the premise that all sterile compounding pharmacies compound only one sterile batch or product per day. This estimate may be flawed as well. Many pharmacies prepare multiple sterile products and batches everyday, with each product or batch incurring over \$800 in testing costs. Patients cannot be expected to pay \$800¹⁹ in testing costs per prescription in addition to expenses sustained through overhead, ingredients, and time of preparation. In addition, if the Board incorporates multiple batches into their estimate for annual compliance costs, the cost to pharmacies and, likewise, the public could exceed \$21 million.²⁰ The Missouri public should not be expected to absorb a cost of \$21 million when a far more effective and cost efficient approach to sterile product regulation may exist.

Further, the Missouri Board of Pharmacy fails to account for the "laboratory testing" or stability studies that it requires in Part (11) "Expiration Dating" Section (C) "Risk Level 3." These studies require a minimum investment of approximately \$10,000 per compounded formulation. The number of compounded formulations that would require testing is virtually unlimited. Requiring stability studies could add significantly to the private entity cost estimates provided.

Given a potential \$20 million cost fluctuation involved in the current annual cost estimates by the Missouri Board of Pharmacy, the regulated pharmacies and the public deserve data to justify and secure the true fiscal impact of these regulations. The Missouri Board of Pharmacy needs to survey state pharmacies, determine the scope of current sterile operations, and solidify the estimates presented in the private entity cost worksheet. IACP would be willing to assist the Missouri Board of Pharmacy in this endeavor.

¹⁵ January 2003 Missouri Register, Page 18, (2)(C)

¹⁶ 260 batches x 45 pharmacies = 11,700 batches. 11,700 batches x \$805 per batch = \$9.4 million.

¹⁷ 260 batches x 61 pharmacies = 15,860 batches. 15,860 batches x \$805 per batch = \$12.8 million.

¹⁸ In addition, these estimates would increase significantly if the testing cost increased to \$925 per batch, as outlined in Footnote 8. Testing costs for 25% (15 pharmacies) would total \$3.6 million. Testing costs for 75% (45 pharmacies) would total almost \$11 million. Testing costs for all 61 pharmacies (100%) would total approximately \$14.7 million. According to these estimate, current cost estimates incur a \$12 million range of uncertainty.

¹⁹ The Missouri Board of Pharmacy's definition of batch includes sterile products, prepared at a discreet time, prepared for a single patient. This could force one patient to incur the entire \$800+ testing cost for the "batch."

²⁰ Estimate based on 2 unique batches or products compounded per day in 75% (45) pharmacies.
2 batches per day x 5 days x 52 weeks = 520 batches. 520 batches x 45 pharmacies = 23,400 batches.
23,400 batches x \$925 per batch = \$21.6 million.

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Due to the severe impact of these regulations on Missouri pharmacies, IACP requests the Missouri Board of Pharmacy to address the concerns outlined in these comments and issue a subsequent draft of the standards for reconsideration by pharmacies and pharmacy stakeholders. These proposed compounding regulations should not be considered with undue haste. The implications and impact of the proposed regulations on Missouri pharmacies warrant provision of additional time for discussion, research, evaluation, and revision.

In addition, the Missouri Board of Pharmacy must make provision in its final draft of these regulations for an appropriate effective or compliance date. Pharmacies will need time to adjust policies, practices, facilities, and equipment to comply with the regulations promulgated by the Missouri Board of Pharmacy.

IACP appreciates the opportunity to share our concerns with the Missouri Board of Pharmacy and we look forward to working with you to continually advance sterile product quality and, likewise, patient health and safety. If we can be of any assistance, or if you have any questions, please do not hesitate to contact me or Jennifer Brashares, IACP's Regulatory Affairs Coordinator, at (281) 933-8400.

Respectfully submitted,

L.D. King
Executive Director

cc: Jennifer Brashares