

76reCOMMONWEALTH OF MASSACHUSETTS
BOARD OF REGISTRATION IN PHARMACY

MINUTES OF THE PHARMACY SUBCOMMITTEE ON ABNORMAL RESULTS

239 Causeway Street, Fourth Floor ~ Room 417A
Boston, Massachusetts 02114

Friday, May 29, 2015

Advisory Subcommittee Members Present

Karen B. Byers, MS, RBP, CBSP (Expert in Microbiology)
Anthony M. Cundell, PhD (Expert in USP<71>): **attended remotely by teleconference**
David H. Farb, PhD (Expert in Clinical Pharmacology): **arrived @ 11:10 a.m.**
Rory K. Geyer, PhD (Expert in cGMT)
Eric Kastango, RPh, MBA, FASHP (Expert in USP<797>): **attended remotely by teleconference**
Antoinette Lavino, RPh, BCOP (Expert in USP<797>)
Francis McAteer (Expert in Microbiology)
John Walczyk, RPh, PharmD (Expert in USP<795>)

Board of Pharmacy Present

Timothy Fensky, RPh, FACA

Support Staff Present

James Lavery, JD, Director, Divisions of Health Professions Licensure
David Sencabaugh, RPh, Executive Director, Board of Pharmacy
Vita Berg, JD, Board Counsel
Timothy St. Laurent, Deputy Director, Divisions of Health Professions Licensure
William Frisch, Jr., RPh, Director of Pharmacy Compliance
Kelly Ann Barnes, RPh, JD, Director of Pharmacy Quality Assurance
Janet Sullivan, Program Coordinator
Joseph Sceppa, RPh, MS, MBA, Pharmacy Consultant

TOPIC:

1. CALL TO ORDER

DISCUSSION: At 10:09 a.m., J. LAVERY, Director, Divisions of Health Professions Licensure, called the second meeting of the Pharmacy Advisory Committee Sub-Committee on Abnormal Results to order. He welcomed Sub-Committee members and thanked them for their commitment. Mr. LAVERY indicated that the meeting was being recorded by the Board and asked if anyone in the audience was recording the meeting. No one indicated they were recording. The 5 members in attendance, K. BYERS, R. GEYER, A. LAVOIE, F. McATEER and J. WALCZYK exceeded the 4 member quorum. A. CUNDELL and E. KASTANGO attended remotely by teleconference.

SubCommittee members and Board staff introduced themselves.

ACTION: So noted.

TOPIC:

2. APPROVAL OF AGENDA

10:13 a.m.

DISCUSSION: J. LAVERY, asked if there were any changes to the tentative agenda. There were not.

ACTION: Motion by J. WALCZYK, seconded by K. BYERS, and voted unanimously to approve the agenda with no changes. D. FARB was not present for the vote.

TOPIC:

3. TOPICS FOR REVIEW/PRESENTATION

10:15 a.m.

DISCUSSION: W. FRISCH, Director of Pharmacy Compliance, distributed a memo to Members of the Advisory Committee “Abnormal Results” Subcommittee: *Proper Response to Environmental Monitoring Results Above USP <797> Action Levels*, May 29, 2015. The memo included a revised flow diagram, “Suspend compounding based on location”. The flow diagram included 5/1/15 Advisory SubCommittee recommendations for ISO-5 USP <797> Action Levels. K. BARNES, Director of Pharmacy Quality Assurance recommended that the SubCommittee focus on options for ISO-7 Buffer Room (POS) outlined in the memo. The objective of the flow diagram would be to describe a series of factors for a pharmacy to consider to appropriately respond to above action levels.

- FM: Indicated that he does not see many ISO-5 “Open” clean rooms or Integrated ISO-5 LFWBs, and that customized interior designs (e.g., locating a LAF Hood on an open steel bench) should be viewed as a red flag.

K. BARNES indicated that in this phase the focus is on the design of the room, the focus on organisms will be addressed later.

- FM: Indicated that investigators focus on a “preponderance of evidence”.
- RG: From the FDA’s perspective, a manufacturer would open a Root Cause Analysis, quarantine the product, and release it only on completion of the investigation. The FDA would ask if a problem with an ISO-5 PEC would lead to an ISO-7 problem. If the problem is limited to the ISO-7 area, then the FDA would consider the history of media fills and personnel monitoring.

K. BARNES asked if the design of the ISO-5 PEC affects the ISO-7 problem.

- RG: Would favor a general approach rather than trying to be more specific.
- AL: Questioned whether literature exists to support design of ISO-5 PEC affecting an ISO-7 excursion.
- EK: Does not believe that data exists that comes to a consensus as to what’s reasonable.
- KB: Recommended that we rely on culturing results.
- RG: FDA guidance doesn’t have data. It varies case-by-case.
- FM: In his experience, 503A pharmacies have a BSC in an ISO-7 room and have a high level of control. Design is not an issue.
- KB: Define “Pause”

K. BARNES indicated that when she uses the word, “Pause”, she expects that compounding would immediately stop. The length of the pause is variable, based on the remediation plan; the facility may do “Dispensing-at-risk”.

W. FRISH has concerns as the Board receives the above-action-level reports 1-2 weeks after an excursion. He would suspend compounding in all 3 ISO-7 Buffer Room (POS) scenarios on the flow chart (Integrated ISO-5 LFWB, Pos. Pressure PEC/CAI, and Neg. Pressure PEC/CACI).

- JW: Likes the idea of a “Speed Bump” for all 3 ISO-7 Buffer Room (POS) scenarios.
- AC: He has sent members a copy of USP <1116>. It refers to a “frequency of isolation” not to exceed a particular amount which is higher as one goes from ISO-5 to ISO-8. He feels that it is an overreaction if the final organism is ISO-7 ?
- RG: Feels that the answer is somewhere in the middle. He agrees with the “Speed Bump” approach. He recommends contacting the Board with a well thought out remediation plan.

If the plan to the Board has red flags, then the Board would call the facility and indicate that they should stop compounding.

K. BARNES agrees with RG but acknowledges that the Board's guidance for pharmacies is not yet available.

- EK: Also likes the idea of a speed bump for excursions in an ISO-7 environment. He noted that USP <797> does define what to do if cfu counts exceed the allowable level: *"Any cfu count that exceeds its respective action level should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garbing or working practices. The source of the problem shall be eliminated, the affected area cleaned, and resampling performed."*

He suggested that we consider a stratified approach. He felt that clinicians in the group would appreciate that to shut down an operation for 1 CFU or an excursion in an ISO-7 room is pretty significant. ISO-7 excursions should be treated differently than ISO-5. USP <797> is not clear on how one should clean as part of remediation.

Maybe the speed bump is put into practice immediately; that you do a robust recleaning with a germicidal and water, followed by a sporicidal detergent and water; sample the site, and limit the BUDs.

Excursion in an ISO-7 environment could be due to a number of things.

J. LAVERY acknowledged the need for a pause and asked if the remediation will answer the question as to how long the pause should last.

K. BARNES recommended that we consider modifying the beyond-use date (BUD) and dispense "at risk". She expressed concern for excursions related to air sampling. She asked what type of remediation is required and acknowledged that remediation should define the appropriate process response as well as whether compounding can continue during the remediation.

W. FRISH noted that some of the compounders are not familiar with the pathogenicity of certain organisms. That is why guidance from the Board is so important.

- AL: Noted that it is important to distinguish between contamination with respect to air and surface sampling. In responding to surface sampling, thorough cleaning, reducing the BUDs, and retesting might be the way to go.

K. BARNES noted that it is not the role of the Board to act as a consultant.

- JW: The size of the speed bump will vary based on the excursion.

J. LAVERY asked members if they were in agreement with the recommendations.

- EK: His understanding is that if there is a speed bump in reaction to a positive test; that the facility cleans, retests, and notifies the Board.
- AC: Feels that we have chosen a good middle position. The surface that poses the greatest risk for contamination are the gloves of the compounder. He is skeptical about giving too much weight to the pathogenicity of the organism cultured. It is rarely organisms like staph aureus that cause infections, but rather organisms that may be considered non-pathogenic, like fungi. The importance of identifying the organism is to ensure that the remediation design is most likely to address the issue.

W. FRISH noted that a flow diagram in his memo identified 3 scenarios for the ISO-7 Buffer Room (POSITIVE): Integrated ISO-5 LFWB, Pos. Pressure PEC / CAI, and Neg. Pressure PEC/CACI.

- All members agreed that the responses would be the same as the positive pressure buffer rooms.
- DF arrived at 11:10 a.m.
- EK: The Board needs to give registrants structure, forms, and an outline of a remediation plan, as they may not be skilled/trained to address microbiological excursions. Registrants

have not had enough experience to be able to utilize professional discretion in addressing remediation of excursions.

- Other Subcommittee members voiced general consensus to EK's recommendation.

W. FRISCH indicated that the Board also receives reports on excursions in Ante Areas and asked if we wanted to include ante areas in the discussion or move them to a parking lot.

K. BARNES felt we should start with ISO-5 surface levels and focus on remediation; what is appropriate?

- AL: In order to support the microbiologists, we need to be able to say which microorganisms are on or not on a pathogenic list.
- RG: Need to force pharmacies to do their own risk assessment. For instance, if they are compounding high-risk level products, for any excursion the firm should say what they are doing and that they are involving a microbiologist.
- AL: Would look to the Board for guidance.

V. BERG reminded the group that it is the responsibility of the pharmacy to provide the plan to the Board staff (rather than the Board). The Board staff needs specific criteria in order to utilize prior delegated authority, and then decide if it needs to be referred to the Board or a Board member. She expressed concern about the Board's ability to react in real time.

- RG: The FDA asks 1) if the firm has redundant capacity (e.g., can 1 line be shut down?) If so, the remediation is easier. 2) The FDA also asks what the patient needs are. They put some emphasis on bugs.
- FM: Noted that at one time the FDA wanted to create a national QA manual. The Board is attempting to create top level guidance, placing the onus on the registrant to create an acceptable plan.

K. BARNES indicated that this process is a learning curve. The Board and registrants need a flow diagram for reference. Registrants need to meet the minimum expectations to ensure patient safety.

W. FRISCH said that some (but not all) pharmacies give a very detailed remediation plan to the Board.

- DF: Noted that trending is an integral piece and asked if the Board has a record of historical excursions.

K. BARNES indicated that the Board does not maintain trending data, but that some registrants may have the data. Having the data would allow a registrant to more appropriately respond to an excursion.

- RG: Clean with appropriate cleaner(s); appropriately sample, and recertify.
- KB: Is the organism the same from the ISO-5 PEC and the ISO-7 area? There is a need to conduct the RCA to determine the nature of the problem.
- RG: The issue is tricky. The manufacturer may have an abundance of monitoring data. FDA focuses on trending. Need results of media fill tests and glove tests.
- AL: This would be hard to do if monitoring is only done once a year.

K. BARNES reminded the group of the need to demonstrate effectiveness of cleaning agent and making sure it is in date.

- KB & AL: It may not be necessary to shut down all compounding; maybe only the single PEC. May dispense at risk; rethink beyond-use date.

K. BARNES reaffirmed the need for more frequent monitoring, especially after an excursion.

However, if it is the right thing to do (to not compound in a specific PEC), then it is the right thing to do.

V. BERG noted that there comes a time when there can be no concession to continue to compound in a specific PEC.

K. BARNES noted that for those facilities with a single PEC, could consider dispensing after cleaning but not before results from resampling. She asked if dispensing at risk with reduced BUDs until testing results are obtained is appropriate.

- KB: Has never had a disinfectant, specific for a particular microorganism, that did not work.
- DF: Does not see the logic of dispensing at-risk for facilities that have only 1 laminar flow hood. He noted that the patient did not have a chance to approve the dispensing. He feels that a facility compounding sterile products needs a backup plan. This may require installing a 2nd laminar flow hood and should be figured into their business model.

K. BARNES indicated that the Board does not want to automatically shut down a facility, especially an institutional facility. She sees it as a delicate balance between risk and continuity of care.

- DF: Recommends disclosing the risk to the physician prior to at-risk dispensing, with subsequent sign-off. He realizes that there are no easy answers, yet has a concern about the dispensing at-risk concept.
- JW: Reminded the group that testing is only a snapshot in time. Once results have been received, products on hand during testing have often been used. There have also been multiple cleanings since the excursion.

K. BARNES noted that USP <797> allows high-risk level products to be dispensed before testing results have been received as long as there is a recall process.

W. FRISCH acknowledged that dispensing occurs from the time of testing and the receipt of abnormal results. He is concerned that there may be a risk that surface contamination could lead to product contamination.

- RG: Wondered if, in addition to remediation, the cause of contamination could be identified.

K. BARNES noted the importance of a root cause analysis.

- AL: Recommended more frequent testing, and that if the retest comes back as positive, the PEC or buffer area should be shut down.

K. BARNES recommended decreasing the BUD for the interim period while changes are taking place. Consider the BUD chart in USP <797> if dispensing at-risk. Perhaps the Board can provide guidance.

- EK: Time and temperature are enemies if the integrity of a product is compromised. Depending on the excursion, if dispensing at-risk any low or medium-risk level products, the high-risk level BUDs should be the default BUDs until the issue is resolved. Perhaps consider the 12 hour low risk-level if possible.
- FM: Supports EK's recommendation.
- EK: Temporarily modifying the BUD would be analogous to driving under NASCAR's yellow flag, yet the race is not stopped. Perhaps a 3-day maximum BUD for a high risk-level medication.
- JW: Cautioned the group that requiring a 3-day BUD in the ambulatory care setting would essentially mean a 1 day BUD when a shipment is received by a patient.
- AC: In February, the FDA issued draft guidelines on mixing, diluting, and repackaging biologic products. The guidelines agree that the BUD should be reduced, rather than stopping production in the event of an excursion, and is endorsed by the FDA.

D. SENCABAUGH observed that there is risk, and that by decreasing the BUD decreases the risk.

LUNCH 12:14 – 1:10 p.m.

J. LAVERY called the SubCommittee to order at 1:10 p.m. All were present.

K. BARNES agreed that tentatively using the high-risk level BUDs for low and medium-risk level products, she wondered about recommendations for high-risk level products until test results are obtained.

- EK: Noted that many hospitals will not be compounding high-risk level products. Of greater concern is achieving (vs. maintaining) sterility. The risk is higher.
- FM: Most high-risk level compounders in MA are 503A pharmacies.

K. BARNES recommended that anticipatory batching be discontinued until testing results have been received. If the excursion is in the PEC, she recommends stopping high risk level compounding completely until the issue is resolved.

- AC: Agreed with EK's position. He recommended ceasing production of high-risk level preparations until a state-of-control (sterility results) could be demonstrated.
- JW: Agrees; shorten to 1 day if a patient truly needed the medication.

J. LAVERY summarized that the most members felt that a firm needs to stop production until they receive acceptable test results.

- EK: Most hospitals do not do high risk-level compounding, except in rare instances. The impact primarily affects community pharmacies that would need to transfer business during the remediation period.
- JW: Indicated concern for out-of-state pharmacies.

Consensus: If a pharmacy performing high-risk level compounding receives a hit in an ISO-5 PEC, there must be a remedial plan and compounding must cease in that ISO-5 PEC until acceptable test results are received.

K. BARNES indicated that enough direction had been provided concerning surface sampling that we could now consider air sampling.

- EK: If the organism is in the air and the facility is compounding high risk-level products then you have to assume that the HEPA filter is damaged. After stopping production, we need an action plan that includes confirmation that the filter has not been compromised. In addition to cleaning and testing, the PEC needs to be recertified to remediation plan. In low and medium risk-level compounding, the exposure site is small. If another PEC is available, it should be used. If not, cleaning with a robust disinfectant is recommended and using a 12° BUD until recertification is confirmed.

K. BARNES indicated that a 12° BUD would not work in the community setting. She asked if it was acceptable to decrease the BUD to that for high-risk level products?

- FM: USP <797> ISO-5 recertification of HEPA filter; low and medium-risk level → High-risk level BUDs.

W. FRISCH expressed concern that a positive air sample indicated that the HEPA filter is not working and wonders why we would allow further compounding until the filter issue has been addressed.

K. BARNES noted that USP <797> indicates to stop compounding, implement continuity-of-care plans. Air sampling engineering control failed; does this increase the risk of product contamination?

- RG: Consider the testing history (for those that have and maintain that information).

K. BARNES indicated that the Board doesn't receive the history of testing, unless there were excursions.

- KB: We often cannot say that the ISO-5 PEC failed until we know that it has failed. It is more likely that there may have been too many people in the area.
- AL: USP <1116> indicates that there is no data to say that positive air sampling is worse that

positive surface sampling.

- AC: With respect to contamination, gloves are the most critical, air is next, and surface is the lowest. He will try to send copies of his colleagues' papers to committee members. USP <797> the requirement is that you don't detect any organisms in air sampling; it doesn't address surfaces and gloves. He feels that the compounder is the greatest source of contamination.
- RG: Directing a question to AC; if an operator has a hit on gloves, can that operator continue to compound?
- AC: In the pharmaceutical industry, personnel are not automatically taken out of practice if they had a positive hit from their gloves. However, he would remove them from practice.
- RG: Low or medium-risk level: hit on an ISO-5 would require a stop. FDA would issue a Form 483 and possibly a warning letter.

J. LAVERY asked if we are saying that if we had a hit in an ISO-5, should we stop? Is this unreasonable?

W. FRISCH indicated we shouldn't be compounding if we have microorganisms.

- KB: In a hospital it would be problematic if there was a shutdown. Notify RPh and others, immediate remediation plan, inside and outside cleaning; environment checked; unnecessary traffic. Don't have biosafety cabinet failures (checked every 6 months).

J. LAVERY asked "Does one size fit all?"

- EK: USP <797> defines an action level for ISO-5 air samples as >1 CFU. If 2 in an ISO-5, the pharmacy should stop production, conduct a PEC assessment 1^o of the engineering control, followed by remediation. If the PEC does not pass, a full RCA must be conducted.

Consensus: If 2 CFUs are found from an ISO-5 air sample, the pharmacy should stop production, conduct a PEC assessment, primarily of the engineering control, followed by remediation. If the PEC does not pass, a full RCA must be conducted.

- KB & AL: Is there severity data on the difference between air and surface contamination in terms of a risk assessment?
- DF: Multiple levels of control; contamination of air, surface, and gloves.
- EK: Know the potential of compounding; reevaluation of compounding personnel work practices (e.g., hygiene, garbing, aseptic technique); retesting gloves, etc.

K. BARNES If the ISO-5 PEC passes a retest, the compounder can start up production again.

- AL: USP <1116>, printed May 1, 2015 refers to ISO-5 excursions >15 CFUs ("too numerous to count"). It was noted that this refers to CGMPs.
- FM: Recommended observing microbiological technicians as they do their work.

K. BARNES assumed that a pharmacy has moved to high-risk level BUDs, if the PEC passes, and remediation is in progress, can you resume compounding? Yes.

- AL: Operating in segregated compounding space?

K. BARNES indicated that Board staff is looking into this practice.

V. BERG indicated that there will be a summary document that will help at our next meeting.

W. FRISCH & K. BARNES indicated that SubCommittee members can send feedback on a draft back to either of them. This would not be prohibited by Open Meeting Regulations.

TOPIC:

4. CLOSING REMARKS

2:18 p.m.

DISCUSSION: J. LAVERY thanked the group for their time and input.

D. SCENCABAUGH recommended that we have an additional SubCommittee meeting before presenting our recommendations to the full Committee. Perhaps a meeting on June 19th or early

on the morning of the full Advisory Committee meeting (June 26). A note will be sent requesting member preferences.

ACTION: So noted.

TOPIC:

5. ADJOURNMENT

2:21 p.m.

DISCUSSION: None.

ACTION: At 2:21 p.m., motion by K. BYERS, seconded by D. FARB, and voted unanimously to adjourn.

Respectfully submitted,

Joseph M. Sceppa, RPh, MS, MBA, Secretary Pro Tem

LIST OF EXHIBITS USED DURING THE MEETING

1. Preliminary Agenda for the May 29, 2015 Pharmacy Advisory SubCommittee Meeting
2. Memo from Kelly Ann Barnes and William Frisch, Jr. to Members of the Advisory Committee "Abnormal Results" Subcommittee: *Proper Response to Environmental Monitoring Results Above USP <797> Action Levels*, May 29, 2015.
3. *Quantitative Risk Modeling in Aseptic Manufacturing*, PDA Journal of Pharmaceutical Science and Technology, September/October, Vol. 60, No. 5, 267-283.
4. *Reducing Hospital-Acquired Infection by Quantitative Risk Modeling of Intravenous Bag Preparation*, PDA Journal of Pharmaceutical Science and Technology, March/April, Vol. 64, No. 2, 82-91.