

COMMONWEALTH 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 1, 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 @ 11:15 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>)

John Walczyk, RPh, PharmD (Expert in USP<795>)

Advisory Subcommittee Members Not Present

Francis McAteer (Expert in Microbiology)

Support Staff Present

James Lavery, JD, Director, Divisions of Health Professions Licensure

David Sencabaugh, RPh, Executive Director, Board of Pharmacy

Heather Engman, JD, MPH, Board of Pharmacy 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: **left @ 2:15 pm**

Janet Sullivan, Program Coordinator

Joseph Sceppa, RPh, MS, MBA, Pharmacy Consultant

TOPIC:

1. CALL TO ORDER

DISCUSSION: At 10:13 a.m., J. LAVERY, Director, Divisions of Health Professions Licensure, called the first meeting of the Pharmacy Advisory Committee Sub-Committee on Abnormal Results to order. He welcomed Sub-Committee members and thanked them for their commitment. The 4 members in attendance, K. BYERS, R. GEYER, A. LAVOIE, and J. WALCZYK constituted a quorum (4 members), as approved at the March 27, 2015 meeting of the full Pharmacy Advisory Committee.

Mr. LAVERY indicated that the meeting was being recorded by the Board and asked if anyone in the audience was also recording the meeting. No one indicated that they were recording. He also introduced Board support staff in attendance.

ACTION: So noted.

TOPIC:

2. APPROVAL OF AGENDA

10:15 a.m.

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

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

TOPIC:

3. REMOTE PARTICIPATION PURSUANT TO THE OPEN MEETING LAW 10:20 a.m.

DISCUSSION: J. LAVERY introduced H. ENGMAN, Board of Pharmacy Counsel who noted that, consistent with the Open Meeting Law, when members participate remotely, a quorum must be in the room and votes must be by roll call.

The 4 members in attendance, K. BYERS, R. GEYER, A. LAVOIE, and J. WALCZYK constituted a quorum (4 members), as approved at the March 27, 2015 meeting of the full Pharmacy Advisory Committee.

ACTION: Motion by J. WALCZAK, seconded by R. GEYER, and voted unanimously to allow remote attendance, A. LAVOIE: In favor, K. BYERS: In favor, R. GEYER: In favor, J.

WALCZAK: In favor. D. FARB was not present for the vote.

J. LAVERY indicated that two SubCommittee members, A. CUNDELL and E. KASTANGO were unable to be present and welcomed their participation by teleconference.

TOPIC:

4. TOPICS FOR REVIEW/PRESENTATION 10:27 a.m.

DISCUSSION: W. FRISCH, Director of Pharmacy Compliance, thanked SubCommittee members for their commitment and recognized the work of the Board staff and public attendees for their attendance. He briefly reviewed highlights of the March 27th meeting.

K. BARNES, Director of Pharmacy Quality Assurance, discussed the April 24, 2015 memo that had been sent to members of the SubCommittee on Abnormal Results. Since USP <797> does not offer guidance to the appropriate response to abnormal results of environmental monitoring, the Board is turning to the SubCommittee for advice. When responding to a report to the Board on abnormal results, the memo questioned 1) at what point is it no longer safe to continue to compound? and 2) if compounding is suspended, what factors determine that it is safe to resume compounding? She described the series of flow chart drafts were included with the memo. Current regulations require reporting of abnormal results.

Microbial Contaminants

Classification	Air Sample	Surface Sample (cfu per contact plate)
ISO Class 5	>1	>3
ISO Class 7	>10	>5
ISO Class 8 (or worse)	>100	>100

Highly pathogenic microorganisms: gram-negative rods, coagulase positive staphylococcus, molds, and yeast = 1 CFU

K. BARNES indicated that, although a tedious process, she recommended that we review the flow charts, box by box.

- AC: Felt that we cannot rely solely on a single monitoring occurrence from a 6-month microbiology report, and that we need a program that makes sense before taking action before decision trees are put in place.

K. BARNES agreed and indicated that we hope to increase the type and frequency of sampling and will be a recommendation to the Board.

- RG: Agreed with AC. If all we have to go on is a single 6 month sample, if the same organism occurred in other areas, it would increase the significance of the finding.

- H. ENGMAN reminded the group that pharmacies need to know specifics of what to do when they receive an actionable level sampling result. She would like clear standards for the Board.
- KB: Attempted to clarify RG's comment, noting the lack of a trend in a single report
 - RG: Indicated that if the contaminant is found throughout the facility, then the firm does not have controls in place to contain that organism. He would still be concerned even if the contaminants do not exceed action levels.
- J. LAVERY suggested that we do plan to increase the frequency of testing from every 6 months and not have to continue to refer to the need to increase the frequency.
- AC: Decision trees which are all-encompassing are too complex. He recommended creating a simple decision tree for the compounding of low risk-level products and adding additional decision trees for the other risk-levels. Then one could select a decision tree most applicable for the specific facility. Trying to put it all in one decision tree would not be user friendly.
- K. BARNES agreed. She indicated that today's handout reflected historical information and will be abbreviated with the SubCommittee's input.
- AL: The risk-level of compounded products may not matter as the product is going into humans. She would be more concerned with the organism found.
 - JW: Agreed with AL.
- K. BARNES described a case of abnormal results (*pseudomonas*) in which remediation reduced, but did not eliminate contaminants. It was felt that the design of the facility may have contributed. The RCA & Plan of Correction indicated that the contaminant came from fluid in the TPN compounder.
- EK: Part of our unique challenge is to remember that reported results are days or weeks old. Without a lot of data points it is hard to determine a state-of-control. The facility saw a blip 5 days ago, and now there is a concern about a recall at this point. Perhaps the contaminant was brought in by an individual. Perhaps it was a result of not doing what they should do (e.g., proper garbing), or various other possibilities. Without that background, it is hard to make a decision based on that limited data. He is concerned that initiating a recall at that point may not be appropriate.
- J. LAVERY indicated that he values this discussion as these are the exact decisions that the Board is faced with.
- W. FRISH indicated that there were a lot of activities going on that may have contributed to the incident. The HEPA filters were all changed as part of the remediation.
- AL: The case described is alarming. However, hospitals are looking at much lower levels of contamination.
- K. BARNES acknowledged AL concerns and noted that these examples are brought up to help illustrate what Board Staff are dealing with and describe situations of loss of control that was highlighted by the root cause analysis in response to abnormal results.
- H. ENGMAN noted that the USP does not indicate what to do with actionable results. It is inferred. Pharmacists are interpreting this differently. We may recommend a particular course of action but receive push-back. However, after a lengthy discussion they do often take our advice.
- KB: *Pseudomonas* would be expected from a sink with an aerator nearby.
 - JW: If more frequently, remediate and test more frequently.
 - RG: In reviewing batch records from manufacturers, if the FDA reacted to every positive result, there wouldn't be any manufacturing. He indicated that we don't have the luxury of shutting down with one actionable finding.
- It is important to investigate all aspects of production and find out if a state-of-control

exists before taking action. When a report such as “We found broken glass or a particular bug” is received, then the FDA starts an investigation if they think it is significant and not automatically call for a recall until all of the information has been analyzed.

- AL: We do not have that type of luxury within a hospital.
- RG: There is a risk analysis that consists of the risk to the patient who receives the product vs. the risk to the patient may not to receive drug (due to a shutdown).

K. BARNES asked if the FDA has flow charts when dealing with abnormal results.

- RG: Indicated that the FDA does not have specific flow charts for the reasons AC mentioned. . Instead they bring subject experts together. They would also consider the impact of pulling the product. The FDA tried flow charts, but there were too many variables. Essentially it is a case-by-case decision. Significance is heightened if the organism made it into the finished product. Action would not be initiated on a single data point.

- EK: Suggested we try to think about the clean room as a patient (holistically). A patient goes to a doctor with symptoms. If the patient has certain symptoms, the physician orders more testing. Some symptoms (e.g., blood sugar >400 mg/dL) require immediate action and more testing to a point in time (return to normal range).

If there are pathogenic bugs in an ISO Level 5 environment, production should stop. Daily sampling should occur for multiple days in a row. Inspection should include observation of garbing; is it OK?; is documentation OK?

In instances, other than highly pathogenic organisms in an ISO Class 5 environment or others that indicate that a patient is at risk, most of the time the facility is operating under a state-of-control and, in his experience, the incident is transitory.

K. BARNES noted that there are various types of compounders, from low to high. May need to suspend for the higher level of risk. Hospitals create bulk packagers (anticipatory compounding).

- AC: Water borne organisms predominate in sterile product recalls. They don’t normally find pathogens (other than staphylococcus aureus) in the compounding/manufacturing environment.

Category of pathogens found: 1) people; 2) environment; and 3) water borne organisms.

The risk is the lack of sterility. The literature on platelet concentrates relative to infection rates associated with high numbers & pathogenicity. Moderate levels of staph epidermidis didn’t cause infections while staph aureus did. It was worse if pathogens were found on the gloves of technicians.

- At 11:15 a.m. David Farb joined the meeting.

K. BARNES asked if the type of compounding is an issue. Suspend or at least modify so that compounding ceases.

H. ENGMAN asked if we should focus on where the results came from.

J. LAVERY asked if during remediation, was compounding suspended or did they quarantine?

- JW: High risk-level vs. low risk-level is the same risk.
- KB: Agreed with JW.

J. LAVERY indicated that it sounds like there shouldn’t be an immediate reaction.

K. BARNES felt that with High Risk-Level products there is a need for caution, and to stop dispensing until remediation and negative results have been completed.

- RG: If ISO 5 actionable level, determine if the firm has a backup plan; if not, that may change the Board’s decision. He acknowledged the difficulty separating manufacturing from dispensing. Have there have been any adverse events and/or complaints; what types of changes have been made in the last 6 months.

W. FRISCH gave the example of the Board receiving a call on Friday afternoon. The Board needs assurances that no product goes out and there is no patient risk. He needs some compounding limitations.

- JW: May want to focus on location and organism. The Risk Level may not matter if the organism is found in an ISO 5 PEC.
- AL: Agree with JW's comment on organism and location as well as AC's comment on an organism exceeding actionable levels. Public safety should be our primary objective. We need to at least meet USP's Action Level recommendation.

K. BARNES indicated that the initial report contain levels. Subsequently receive a report on organism specificity. ISO 5: Suspend compounding in the affected PEC.

- AC: Disagreed with K. BARNES. Some low risk compounding on a table or the patient's bedside. There needs to be a formal risk analysis to determine what is causing the problem. Organisms on the technician's gloves represent the highest risk. He feels that environmental monitoring is not a perfect tool. The problem is that organisms are isolated, not necessarily the type of organism.
- AL: Agrees, yet needs to take action when contamination is found (e.g., Root Cause Analyses) take time.

J. LAVERY said that we discussed good points and asked if we should vote on any of them.

- AC: Indicated that he works on a lot of committees and task forces. They rarely vote. They discuss an issue and try to reach a consensus (since individuals may not agree on everything).
- DF: Asked about internal process control. People can work in an environment of pathogens and not necessarily contaminate. He recommended comparing internal control sampling with the results of monitoring and if both are (+) and then act.
- AL: Felt that DF's comments make sense. However, process validation is not being done in the majority of facilities.

J. LAVERY indicated that inspectors need specifics so that appropriate action can be taken.

K. BARNES indicated that inspectors need a history of testing as bugs change throughout the year.

- RG: Indicated that he felt comfortable in a worst-case scenario, halting compounding if the organism is cultured in the PEC, unless more patient harm would occur from stopping production.

H. ENGMAN understands that the SubCommittee feels that production should be stopped if the offending organism is cultured from the PEC. In addition, we need to determine what is happening and what remediation is possible.

BREAK 12:00 – 12:49 p.m.

J. LAVERY reassembled the SubCommittee. All were present except A. CUNDELL, who returned at 1:05 p.m.

K. BARNES summarized her understanding of consensus:

- Environmental monitoring in an ISO 5 environment would cease compounding. If the room is the ISO 5 environment, all compounding in the room would cease.
- Surface contamination should be treated differently from air contamination
- EK: Struggles with this issue since contamination by personnel is the most common problem. He indicated that there is a misnomer in considering the whole room as ISO Class

5; it is only that zone in which the registrant can show unidirectional air flow.

- Consensus: A positive culture in an open area ISO 5 room (unidirectional airflow velocity) would require a stop in production, investigation, and remediation.

- KB: Indicated that surface remediation is quick and easy.
- JW: Asked about how long the remediation might take.
- KB: There is a greater concern if there is air contamination vs. surface contamination. Documentation is not as easy.

J.SCEPPA noted that a great many hospitals operate with a single laminar flow hood and encouraged the group to consider the impact of shutting down production in such a facility.

- RG: There is a public health risk of a shutdown. The firm needs to be allowed to show the impact of a shutdown and provide legitimate reasons as to why they should be allowed to continue.
- DF: What is in the public interest. There is a problem if there is a lack of redundancy. Redundancy makes it easier to create a remediation plan.
- AC: Returned to the meeting at 1:05 p.m.

K. BARNES stated that a (+) test indicates that it is unsafe to compound. Then we need to decide whether or not to suspend compounding or that the facility may compound at risk.

J. LAVERY expressed concern about “one size fits all” decisions. He questioned whether we need to separate hospitals from large manufacturing facilities.

H. ENGMAN noted that the USP now has lots of “shoulds”. If there is a (+) finding in a PEC, stop compounding until further notice unless they receive written notice from the Board to go forward. Separate out surface from air contamination.

- JW: What is the remediation plan? He feels that hospitals and manufacturing facilities should be held to the same standard.
- There was lots of general discussion about remediation.

D. SENCABAUGH suggested that we try to get a sense of the meeting on two issues:

- 1) What to do with a positive test in an ISO 5 environment
- 2) Consider a remediation plan

- AC: Disagrees that manufacturing has to cease based on a single actionable level. USP <1116> frequency of isolation within ISO Class 5 areas is expected to be <1%, not 0%. Facilities will isolate organisms on occasion. Test methods can be contaminated. He has concern for the Board if they mandated production to stop based on a single isolated excursion. No pharmaceutical company would stop production based on an isolated positive test result. The FDA would not cite a facility for a single excursion. The facility needs an investigation to determine if the finding is representative of a problem.
- AL: If monthly testing, then if a (+) test -> remediation, investigation, add monthly monitoring, then decide on a state-of-control.
- AC: Agreed with AL.
- DF: Sense of the meeting: If there is a positive test, then something must be done.

W. FRISCH commented that we have some very good compounders who want to do the right thing but do not have enough information to say they are in a state-of-control. A remediation protocol might indicate what would change. The USP mandates action with action levels, but does not indicate what that action should be.

H. ENGMAN: Is hearing that if there is (+) test, the pharmacy needs to stop and do something.

W. FRISCH indicated that some facilities do enough testing to demonstrate a good control of the Environment even if there is an excursion.

- JW: There is a choice: 1) stop/slow down production if they can't prove otherwise, 2) 1 data point: stop, remediate, restart with results

- EK: Some pharmacies have designed entire rooms as ISO Class 5.
- AC: Normally there is a mechanism to separate the operator from the product. This is different in a large room designated as ISO Class 5.

J. LAVERY: Sense of the Meeting: In response to a (+) test in an ISO 5 environment, stop production in a facility is doing the minimum (every 6 month monitoring). This may be an incentive to monitor more frequently.

- AC: Actionable events; need to be investigated and remediated. He does not see the need to stop production of low risk-level compounds.

H. ENGMAN feels that it is likely that regulations will require monthly or bimonthly monitoring. A (+) test should trigger an immediate response.

- JW: High risk-level products have the advantage of going through a final filter with a bubble point.
- EK: Filtering a solution through a 0.22micron filter is not foolproof as endotoxins may pass through them. Low risk-level compounding is a much more closed system.
- JW: Need to stop and think about the next step.
- RG: A hit in an ISO 5 PEC is a red flag and the pharmacy should stop production. A lot of manufacturers will stop production or will not release product until they receive negative results.
- DG: When a radiation badge has one (1) hit, the individual is removed and the radiation lab is shut down.

J. LAVERY seems that after a (+) finding that you have to stop compounding. He indicated that regulators are in a difficult position and need to make informed decisions. Pharmacies need to take responsibility. Some pharmacies/ pharmacists are not up to par.

W. FRISCH said that, unless they know that the pharmacy has the problem under control with additional testing, inspectors cannot arbitrarily allow production to continue.

H. ENGMAN suggested that we break out surface vs. air contamination.

- AC: Concedes if high risk-level; need to cease production
- AL: What if the pharmacy is monitoring frequently. She also has concerns about hospital pharmacy.
- AC: Need to consider if there is a trend between inspection and environmental monitoring. Often this is a systemic problem and an inspector often finds multiple infractions.

J. LAVERY reminded the group that pharmacies need to be informed about what needs to be done. Sense of the Meeting: Excursion: stop compounding What should the pharmacy do to get back into production?

- AC: Agree with the sense of the meeting, it will be more proactive.

K. BARNES indicated that the guidance needs to be published. If we don't say "stop", some pharmacies won't stop. She indicated that the mandatory reporting form and subsequent follow-up is on the Board's web site.

J. LAVERY noted that manufacturers have trending data and contingency plans in place; small pharmacies do not. He also mentioned that after all our work is done, there will be a public hearing. He then asked the group for each of their closing comments:

- 1) AL: Agreed; hospitals need guidance as to what pharmacists should do. USP <797> is not clear (after excursion, consult a microbiologist).
- 2) DG: Supports more frequent testing and communication off the standards. Stop; suspend production in that PEC, follow best practices. In that way, pharmacies will be proactive with a plan of remediation.
- 3) KB: Comfortable with enforced remediation. Concern about stopping production in that it

is not a simple decision.

- 4) JW: Agrees with the direction; decision from flow chart submitted to the Board
- 5) RG: Agrees; speed bump for good compounding companies, problems for the bad. Remediation plans could differ based on the facility.
- 6) AC: Still thinks that environmental monitoring is not a good tool. If the Board can provide guidelines for investigation and remediation, then compounders will be able to meet the regulations
- 7) EK: Mirrors a lot of comments. If you are in the business of sterile compounding, it needs to be taken more seriously, and need to understand the shortcomings of USP <797>. Important to recognize that it is the responsibility of the manager of record (MOR). They need to focus on all of the things that combine to demonstrate a state-of-control. Excursions happen. Quality must be built into the process as opposed to a reaction to problem. Remediation is the way to get back into compliance.

TOPIC:

5. CLOSING REMARKS

2:20 p.m.

DISCUSSION: J. LAVERY thanked the members for their help and commitment of time. What we are doing now will have a great impact on the future. He noted that the process was painful but quite productive.

W. FRISCH also thanked the group and indicated that he had learned a lot through the process. The goal of the Board is not to micromanage pharmacies but to give guidance.

H. ENGMAN recommended that we have an additional SubCommittee meeting before presenting our recommendations to the full Committee. The group agreed.

ACTION: So noted.

TOPIC:

6. ADJOURNMENT

2:38 p.m.

DISCUSSION: None.

ACTION: At 2:38 p.m., motion by D. FARB, seconded by A. LAVINO, and voted unanimously to adjourn.

LIST OF EXHIBITS USED DURING THE MEETING

1. Preliminary Agenda for the May 1, 2015 Pharmacy Advisory SubCommittee Meeting
2. Memo from Kelly Ann Barnes and William Frisch, Jr. to Members of the Advisory Committee "Abnormal Results" Subcommittee: *Development of Guidance for Proper Response to Environmental Monitoring Results above USP <797> Action Levels ("abnormal results")*, April 24, 2015

Respectfully submitted,

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