CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Subcommittee on Antifungal Susceptibility Tests
18 September 2013
1:00 pm (US Eastern Time)

Summary Minutes

A Web conference with the Subcommittee on Antifungal Susceptibility Tests was held on Wednesday, 18 September, beginning at1:00 PM Eastern (US) time. The following participated on the Web conference.

Members

Mahmoud A. Ghannoum, MSc, PhD, EMBA **Chairholder**	**Case Western Reserve University**
Barbara D. Alexander, MD, MHS **Vice Chairholder**	**Duke University Medical Center**
Sharon K. Cullen, BS, RAC	Siemens Healthcare Diagnostics, Inc.
Ana Espinel-Ingroff, PhD	VCU Medical Center
Annette W. Fothergill, MA, MBA, MT(ASCP)	University of Texas Health Science Center
Michael LaFleur, PhD	Arietis
Shawn R. Lockhart, PhD, D(ABMM)	Centers for Disease Control and Prevention
David S. Perlin, PhD	New Jersey Medical School-UMDNJ
Michael A. Pfaller, MD	University of Iowa College of Medicine
Nancy L. Wengenack, PhD, D(ABMM), FIDSA	Mayo Clinic
Peter R. Williamson, MD, PhD	National Institutes of Health

Members Absent (with notice)

Jacques F. Meis, MD, PhD	Canisius Wilhelmina Hospital
Neil S. Ryder, PhD	Concord, Massachusetts

Advisors

David Andes, MD	University of Wisconsin
Nkechi Azie, MD	Astellas Pharma
Lynette Y. Berkely, PhD	FDA CDER
Mariana Castanheira, PhD	JMI Laboratories
Kimberly E. Hanson, MD	University of Utah and ARUP Laboratories
Elizabeth M. Johnson, PhD	The HPA Centre for Infections
Cynthia C. Knapp, MS	Thermo Fisher Scientific
Mary R. Motyl, PhD, D(ABMM)	Merck Sharp & Dohme Corp.
Pranab K. Mukherjee, PhD	Case Western Reserve University
Ribhi M. Shawar, PhD, D(ABMM)	FDA Ctr. Devices/Rad. Health
Yvonne Shea, MS	FDA Ctr. for Devices/Rad. Health (CDRH)
Sean X. Zhang, MD, PhD	The Johns Hopkins Hospital

Reviewers

Philippe Dufresne, PhD	Institut National de Santé Publique
Thomas R. Fritsche, MD, PhD	Marshfield Clinic
Jeff Fuller, PhD, FCCM, ABMM	Alberta Health Services
Beth P. Goldstein, PhD	Beth Goldstein Consultant
William W. Gregory, PhD	Pfizer, Inc.
Laura Kovanda	Astellas Pharma
Shawn Messer, MS, MPH	JMI Laboratories
A. Brian Mochon, PhD, D(ABMM)	Banner Gateway Medical Center/Laboratory Sciences of Arizona
Rene Pelletier, MD, FRCP	Centre Hospitalier Universitaire de Quebec
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiology Institute

Guests

Monique Fouant	Astellas Pharma
Roberta Knefel	bioMérieux, Inc.
Kerry Snow	FDA
Peter Warn, PhD	Euprotec
Collette Wehr	Siemens Healthcare Diagnostics
Nathan P. Wiederhold, Pharm.D.	UT Health Science Center

Staff Present

Tracy A. Dooley, BS, MLT(ASCP)
Marcy L. Hackenbrack, MCM, M(ASCP), BA

Meeting Materials Provided Prior to Meeting

- Agenda
  - Use of recording secretaries for January meeting
  - Overview of new CLSI voting process
  - Review of Tier 3 QC data
  - Review of QC ranges for *Candida* spp. and isavuconazole
- Tier 3 QC data tables
- *Candida*/Astellas presentation

Purpose of Meeting

The purpose of the meeting was to review and discuss data for inclusion in the next revision of the antifungal susceptibility testing documents in preparation for the January 2014 meeting.

Opening Remarks

Dr. Ghannoum opened the meeting at 1:05 PM Eastern (US) time by thanking the participants for joining the Web conference. Ms. Hackenbrack called the role for members and advisors and requested that any additional participants send her an email indicating that they were present on the call.
Ms. Hackenbrack discussed the possibility of using subcommittee participants as recording secretaries during face-to-face meetings. She stated that recording secretaries are being utilized by the working groups under the Antimicrobial Susceptibility Testing Subcommittee and the program has been very successful. She stated that the recording secretaries would be required to take notes during one or more presentations at face-to-face meetings. The information to be recorded would include the main points of discussion on a particular presentation, the rationale for any decisions, and results of votes. These notes will be forwarded to Ms. Hackenbrack for incorporation into the official summary minutes. Anyone interested in volunteering to assist as a recording secretary should contact Ms. Hackenbrack. The number of volunteers and agenda items will dictate the number of presentations for which each volunteer will be responsible. **Note:** Advisors or reviewers who have been appointed as recording secretaries may be eligible for reimbursement for travel to the meeting.

Ms. Hackenbrack provided an overview of the new, two-stage document voting and review process. She reported that all documents that have not yet begun the voting will move into the new process. The voting stages will be as follows:

- **First voting stage** (60 day review and vote followed by a 60 day comment resolution and editorial review period)
  - Review, comment, and vote by the document development committee/subcommittee
  - Review, comment, and vote by CLSI member delegates
  - Review and comment by the appropriate consensus committee
  - Review and comment by the general public

- **Second voting stage** (15 day consensus vote followed by 30 day period for preparation for publication)
  - Vote only for approval to publish by appropriate consensus committee
  - Editorial issues will be resolved by CLSI staff. Minor issues will be addressed during the next revision cycle. Only major technical errors or issues will be addressed and will require a second 60 day vote

It is expected that the document being submitted at the first voting stage will be in its final, complete form. Revisions will be in response to comments submitted during the 60 day review period. The committee authoring the document (eg, subcommittee working group or document development committee) and all commenters will have the opportunity to review the resolutions to the comments and the revisions made in response to those comments. This review will occur before the document continues in the consensus process. The committee and reviewerwill be expected to acknowledge the revisions and resolutions or submit an appeal.

Ms. Hackenbrack stated that she will provide more detailed information and a flow chart of the new process during the January 2014 meeting.

Meeting Discussion

The substantive discussion points of the meeting are listed below (see Table).

Agenda Topic		Committee Discussion Points and Rational for Decisions Made and/or path Forward
1.	Review of Tier 3 QC data (Ms. Cullen)	• Ms. Cullen provided an overview of the tier 3 QC data collected from participating laboratories. She stated that the purpose of collecting the data was to review the QC ranges and determine if any adjustments need to be made. Based on the data collected, she noted the following: – For *Candida krusei*, adjustments of the ranges for caspofungin, and anidulafungin may be needed. – For *Candida parapsilosis*, adjustments of the ranges for posaconazole, itraconazole, and caspofungin. • Dr. Motyl commented that it appears that a relatively small set of data was collected and may not be sufficient to make informed decisions on the ranges. Ms. Cullen reviewed the requirements specified by CLSI document M23 (*Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters*) and indicated that the data sets are considered sufficient as outlined in M23. There was also some discussion regarding the fact that one or two laboratory's data accounted for the majority of the data and the other laboratory's numbers were quite small. It was noted that additional data should be requested to reduce potential bias due to one laboratory providing the majority of the data. • The participants agreed with Dr. Motyl's assessment and decided that additional data should be collected and reviewed and may also be analyzed by the range finder method prior to making any decisions. • Ms. Cullen stated that she will send a list of drugs that require additional data and Ms. Hackenbrack will distribute the request to the subcommittee. Ms. Cullen also requested that testing laboratories provide information on drug lot numbers. All data should be submitted in time for collation and distribution as background for the January 2014 meeting (**Note**: The deadline for submission of background material for the January 2014 meeting will be distributed in the near future).
2.	Discussion of issues with caspofungin QC	• Specific issues regarding the QC ranges for caspofungin were discussed. It has been noted that there is much interlab variation in the MIC distributions for caspofungin with results at the extreme edges of the ranges. Since clinical breakpoints are based on these ranges, patient results may be affected. • Dr. Motyl stated that she recently discussed this issue with Dr. Arendrup and other representatives of EUCAST. She reported that she has reviewed the issue within her organization and believes that because of stringent QC performed during manufacturing, the problems are not related to the drug quality. It was agreed that this issue needs to be studied further to determine the causes and to find a method for correcting it. • It was suggested that new multicenter MIC data with acceptable interlab reproducibility is needed and that QC organisms that will produce more stable results may need to be identified. • Dr. Motyl proposed that this issue be discussed further during the January meeting. Dr. Motyl reported that Merck is working independently with select experts for guidance on

		this problem and that her organization will present the findings of their investigation at the January meeting. Dr. Alexander proposed that a small *ad hoc* working group be formed to meet by conference call to help brainstorm the issue before the January meeting.
3.	Presentation of results of an interlaboratory study for the identification of QC strains for testing isavuconazole against *Candida* (Dr. Ghannoum)	• Dr. Ghannoum presented the results of an interlaboratory study performed to obtain additional 24 hour isavuconazole MIC data for two potential QC strains to be included in the revision of M27-A3. Based on the data, the following conclusions were made: – Laboratory 8 was interpreted as an outlier based on its out-of-range data for voriconazole and its data was excluded. – *C. parapsilosis* ATCC® 22019 and *C. krusei* ATCC® 6258 are proposed as the QC strains to be included in the revision of M27 – A 50% inhibition endpoint is recommended for isavuconazole in order to be consistent with other azoles listed in M27. – The proposed QC ranges recommended for *C. parapsilosis* ATCC® 22019 were: o 24 hr – 0.015 – 0.06 µg/mL o 48 hr – 0.03 – 0.12 µg/mL – The proposed QC ranges recommended for *C. krusei* ATCC® 6258 were: o 24 hr – 0.06 – 0.5 µg/mL o 48 hr – 0.12 – 0.5 µg/mL • Concern was raised regarding the 48 hr/50% inhibition data generated by Laboratory 8. It was suggested that this data should be studied further. It was noted that the current data suggests a three dilution range for *C. parapsilosis* at 48 hours whereas the prior data presented at the January 2013 meeting suggested a four dilution range for *C. parapsilosis* (0.015-0.12 µg/mL) at 48 hours. It was suggested that data presented at the January 2013 meeting be combined with the current data to determine whether the QC range should be three or four dilutions. It was agreed that all data (16 laboratories) would be examined, combined, and presented at the January 2014 meeting. • A motion to approve 24 hr QC ranges was made and seconded. The vote to approve the ranges (*C. parapsilosis* ATCC® 22019: 24 hr - 0.015 – 0.06 µg/mL and *C. krusei* ATCC® 6258: 24 hr - 0.06 – 0.5 µg/mL) was passed (**9-0; 2 absent**).
4.	Discussion of ECV values for isavuconazole and echinocandins with *Aspergillus* spp. and for *Cryptococcus neoformans* and *Cryptococcus gattii* with the azoles, amphotericin B, and flucytosine	• Dr. Ghannoum stated that the discussion and decisions on ECVs will be tabled until the January 2014 meeting. This will allow Dr. Pfaller and Dr. Espinel-Ingroff to organize the data for easy review.
5.	Other business	• It was noted that in M27-S4 that it is recommended that echinocandins results be read at

		24 hr; however, both 24 and 48 hr QC ranges are provided. It was recommended that a footnote be added to explain that users should rely on the 24 hr QC ranges when reading results at 24 hrs and on 48 hr QC ranges when reading results at 48 hrs. • It was agreed that a footnote should be added to the next edition.

Action Items – Due by Friday, 6 December 2014

Specific Action Item Descriptions		Responsible Individual (NOTE: Include Date if different from above)
1.	Submit interest in serving as a recording secretary for the January 2014 meeting	Interested subcommittee member, advisor, or reviewer
2.	Provide a list of organisms and criteria for additional QC data; and Distribute request for QC data for presentation in January	Ms. Cullen Ms. Hackenbrack
3.	Formation of an ad hoc working group to study the caspofungin QC issue	To be determined
4.	Consolidate isavuconazole 48 hr QC data from all 16 laboratories to present at the January meeting	Dr. Ghannoum
5.	Reorganize all ECV data and provide a presentation for the January meeting	Dr. Pfaller Dr. Espinel-Ingroff

Next Meeting Reminder:

The next meeting is scheduled for **Saturday, 11 January 2014 in San Antonio, Texas**. A formal announcement and registration information will be distributed in the near future. Specific agenda and reference materials for discussion will be distributed prior to the meeting. All agenda materials should be submitted by **Friday, 6 December 2013**. The main purpose of the next meeting is to complete the action items from the current Web conference, to review and vote on ECVs, discuss the caspofungin QC issue, and discuss revision of all antifungal documents.

Adjournment

Dr. Ghannoum thanked the participants for their time and dedication. The meeting was adjourned at 3:00 PM Eastern (US) time.

Respectfully submitted,

Marcy L. Hackenbrack, MCM, M(ASCP)
CLSI