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Subcommittee on Antifungal Susceptibility Tests
Agenda/Summary Minutes

Meeting Title:	Subcommittee on Antifungal Susceptibility Tests	**Contact:**	Marcy Hackenbrack
Meeting Date:	Saturday, 10 January 2015	**Secretary:**	Philip Dufresne
Start Time:	8:00 AM Eastern (US) time	**End Time:**	4:30 PM Eastern (US) time
Meeting Purpose:	Annual meeting to review Antifungal subcommittee projects and new susceptibility data		
Requested Attendee(s):	Chairholder, Vice-chairholder, Members, Advisors, and Reviewers of the Antifungal Subcommittee and any interested guests		
Actual Attendee(s):	B. Alexander, M. Ghannoum, M. Castanheira, A. Espinel-Ingroff, A. Fothergill, L. Kovanda, M. LaFleur, S. Lockhart, J. Meis, D. Perlin, N. Wengenack, D. Andes, L. Berkeley, P. Dufresne, K. Hanson, C. Knapp, G. Procop, R. Shawar, M. Traczewski, N. Wiederhold, S. Brown, J. Fuller, D. Getsinger, B. Goldstein, P. Hogan, R. Jones, S. Killian, M. Mansfield, M. Motyl, R. Rennie, D. Shortridge, J. Turnidge, M. Arndt, Amit Desai, R. Eusebio, G. Ewald-Saldana, N. Holliday, S. Jang, R. Knefel, J. Kus, B. Ling, S. Maysent, S. Nambiar, J. O'Connor, N. Robles Hernandez, K. Sei, S. Shurland, S. Moser, D. Schwab, T. Dooley, M. Hackenbrack		

AGENDA

Item	Time	Presenter	Description
1	8:00 am	Dr. Alexander	Opening Remarks
2	8:05 am	Glen Fine	CLSI Board policy update
3	8:20 am	Dr. Alexander	Annual Subcommittee Update (Presentation) • Vote: January 2014 meeting summary • Vote: May 2014 meeting summary
4	8:40 am	Dr. Ghannoum Dr. Lockhart	Update on development of M57 and supplement (Timeline; Draft document and supplement) • Publication timeline review – Scheduled for October 2015 • Discussion of supplement contents
	9:00 am	**Break**	
5	9:15 am	Dr. Lockhart	Discussion of ECV Raw Data Repository • Repository host • Permanent ECV working group/quarterly updates • Access to data
6	10:15am	Dr. Alexander Dr. Turnidge	Analysis plan for ECV determination (2 Excel files) • Review of methods • Availability of Range Finder for analysis
7	11:15am	Dr. Alexander	Re-review and re-vote on *Candida* and *Aspergillus* ECVs (Tables)
8	11:50am	Dr. Alexander	Plan and timing for review and vote on *Cryptococcus* ECVs – Vote by May 2015 or postpone to October 2015?

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Item	**Time**	**Presenter**	**Description**
	12:00pm	**Luncheon**	
9	1:00pm	Dr. Alexander	Updates: Revision of M27 and M38; Development of M27/M44 and M38/M51 • Timeline to publication; Submissions on hold until M57 is complete • M38/51 Supplement contents (Jeff Fuller) • Siemens queries and points for clarification (Alexander)
10	1:45 pm	Dr. Perlin	Caspofungin working group update (Protocol) • Sort through variable impacting caspofungin testing • Identifying new QC isolates to monitor echinocandin susceptibility
	2:45 pm	**Break**	
11	3:00 pm	Dr. Andes Dr. Kovanda	Isavuconazole interpretive breakpoints for *Aspergillus* spp. (Presentation)
12	3:45 pm	Ms. Cullen	Tier 3 QC data review (Excel file)
13	4:15 pm	Dr. Alexander	Other business
14	4:25 pm	Dr. Alexander	Closing remarks • Spring 2015 conference call? • Next meeting: Saturday, 9 January 2016 in Tempe, Arizona
15	4:30 pm	Dr. Alexander	Adjournment

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1.	**Opening Remarks (B. Alexander)** Dr. Alexander welcomed all to the annual Subcommittee on Antifungal Tests (AFST) meeting.
2.	**CLSI Board policy update (G. Fine)** Glen Fine, CEO of the CLSI introduced himself and Luann Ochs. He announced that the CLSI Board had recently changed the policy regarding participation of pharmaceutical representatives as voting members on susceptibility subcommittees. • Representatives of pharmaceutical companies and ancillary industries will no longer be allowed to serve as "Voting Members". • The aim is to better align CLSI with FDA rules and legislation at the national level. Voting members from the pharmaceutical industry were sometimes put in an awkward position when voting on antimicrobial agent breakpoints for drugs developed by their employers. The new policy will ensure that there is no perceived conflict of interest between CLSI and pharmaceutical companies. The image integrity and independence of the CLSI committees will be reinforced. • This policy change applies to pharmaceutical subconstituency and ancillary industries who represent pharmaceutical companies when presenting breakpoints but not to members of other industries (eg. manufacturers of antibiotic panels or other). Participation on working groups will not be affected. CLSI will listen to any comments or suggestions and requested that AFST participants forward any comments to CLSI regarding this policy change.
3.	**Annual Subcommittee Update (B. Alexander)** Dr. Alexander summarized the current AFST membership (members and advisors). – Two new members were rotated on in mid-2014: Dr. Castanheira (JMI) and Dr. Lafleur (Arietis) – Five members have completed their 4 year terms and are scheduled to rotate off in 2016. Due to new the CLSI policy change regarding voting member constituencies, some of pharmaceutical industry members will also need to be replaced in 2016 (Dr. Castanheira, L. Kovanda [Astellas] and M. LaFleur (Arietis). Accordingly, and in order to retain experience on the committee, Dr Alexander may ask some members whose terms expire in 2016 to extend their tenure as voting members by one year. All voting members were asked to introduce themselves and disclose conflict of interest, if any. Dr. Alexander asked that her DOI statement be updated to reflect research grants from Synexis, and Viamet Pharmaceuticals and that she serves as a site investigator for clinical trials sponsored by Synexis, Gilead and Chimerix. Ten out of 11 members were present. A minimum of seven affirmative votes was required to pass a motion/vote. Dr Alexander reviewed the document process (eg, e-mail voting procedure, voting rules, etc). A vote was requested for the summary minutes of the May 2014 Web conference. It was noted that the January 2014 meeting summary minutes had been approved during the May 2014 Web conference. – *Vote: May 2014 meeting summary* (document 03C) –Accepted with minor correction to minutes. Posaconazole/*Aspergillus fumigatus,* 97.5% statistical ECV was changed from 0.5 to 0.25 mg/L (10-0)

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Item 3 (cont)

Dr. Alexander summarized the status of the AFST projects:

- **M27-A3 (2008):** *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*.
  - Currently under revision
  - Working group: S. Lockhart and L. Kovanda
  - This document refers to M57 (*Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing*). Publication of M27-A4 will be deferred until M57 is published (expected by January 2016)
  - Timeline: Complete M27-A4 draft by May 2015; Prepare for vote in Fall 2015 and submit for vote as soon as M57/M57-S is published. Expected publication in July 2016.

- **M27-S4 (2012)/M44-S3 (2009)**: Informational supplements for M27 and M44
  - Currently in revision process: M27-S4 and M44-S3 will be combined to form a single supplement (M27/M44-S).
  - Working group: B. Alexander and A. Fothergill
  - This supplement to be published simultaneously with M27-A4.
  - Timeline: Complete M27/M44-S draft by May 2015; Prepare for vote in Fall 2015 and submit for vote as soon as M57/M57-S is published. Expected publication in July 2016.

- **M44-A2 (2009):** *Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts*.
  - Reviewed and reaffirmed by M. Traczewski and M. Motyl in May 2014.
  - Any minor revisions that are needed can be included in the new combined supplement (M27/M44-S).

- **M38-A2 (2008):** *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi*
  - Currently in revision process.
  - Working group: A. Espinel-Ingroff and P. Dufresne
  - Since this document refers to M57, publication of M38-A3 will be deferred until M57 is published (expected by January 2016)
  - Timeline: Complete M38 draft by May 2015; Prepare for vote in Fall 2015 and submit for vote as soon as M57/M57-S is published. Expected publication in July 2016.

- **M38-S (no current version)/M51-S (2010): Informational supplements for M38 and M51.**
  - New document to be created as single supplement to M38 and M51.
  - Working group: M. Ghannoum and J. Fuller
  - This supplement to be published simultaneously with M38-A3.
  - May include only QC and other supplementary information (no breakpoints).
  - Timeline: Complete draft by May 2015; Prepare for vote in Fall 2015 and submit for vote as soon as M57/M57-S is published. Expected publication in July 2016.

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	Item 3 (cont). • **M51 (2010):** *Method for Antifungal Disk Diffusion Susceptibility Testing of Nondermatophyte Filamentous Fungi* – Reviewed and reaffirmed by M. Traczewski and M. Motyl in May 2014. – Minor revisions required that can be included in supplement revision. • **M57 and M57-S (no current versions):** *Principle and Procedures for the Development of Epidemiologic Cutoff Values for Antifungal Susceptibility Testing* – New documents – Working group: M Ghannoum (Chair), M. Caveling-Arendrup, S. Brown, A. Espinel-Ingroff, S. Lockhart, M. Motyl, J. Turnridge – New supplement to include ECVs for yeasts and filamentous fungi (first version will contain ECVs for *Candida* spp. and *Aspergillus* spp.) – Timeline: o M57 draft is almost completed and should be finalized in February 2015; Draft will be prepared for vote once the supplement is completed o ECVs need to be re-reviewed and another vote will be required due to issues with consistency in the method for determining the values that had been approved in the past o A Web conference will be scheduled for April 2015 to re-vote and finalize all ECVs that will be included in the supplement o The supplement will be reviewed and finalized in July 2015 and prepared for vote in conjunction with the M57 draft. o Publication for both is expected in or before January 2016. Next annual AFST meeting will be held on 9 January 2016 at the Mission Palms in Tempe, Arizona. A poll for the April 2015 Web conference will be distributed in the near future.
4.	**Update on development of M57 and supplement** (M. Ghannoum and S. Lockhart) Dr Ghannoum reported the progress made at the working group meeting held on 8 January 2015. • The draft was finalized with the comments received from the working group members. He expressed gratitude for all feedback. • The document was reorganized and major revisions were completed in order to make it as simple, clear and concise as possible. Once revisions discussed during the meeting are completed, the draft will be circulated for final review by the working group in February. Official voting by the AFST will not be initiated until voting on the ECVs are completed (April 2015) and the supplement has been reviewed and finalized. • Since the AFST is ahead of Subcommittees on Antimicrobial Susceptibility Testing and Veterinary Antimicrobial Susceptibility Testing regarding the development and use of ECVs, efforts will need to be coordinated to ensure consistent language and approach in all susceptibility testing documents. It was agreed that the M57 Draft will be shared with these groups to facilitate concordance with language and methods.

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	Item 4 (cont). • Efforts will be made to educate the community with regards to ECVs. – When M57 is published, a Webinar can be scheduled by CLSI to educate users on ECVs and promote their use. – Dr. Ghannoum will contact ASM, the Infectious Disease Society of America (IDSA), and ICAAC to propose a symposium or webinar. Dr. Lockhart reviewed the plan forward for M57 and its supplement. • The M57 draft will be finalized by February. • Once all ECVs are finalized by the ASFT in April, the supplement will be prepared and distributed for review by the working group. • Once finalized, the draft and its supplement will be prepared for the proposed vote in June or July. Publication is expected by January 2016. • M57 aims to explain ECV language clearly and to provide clinical guidance to microbiologists so that ECVs are understood by clinicians. • 97.5% statistical ECVs using ECOFF finder (Dr. Turnridge) will be used to determine all ECVs for M57. • The first supplement will be restricted to ECVs for *Aspergillus* and *Candida* spp.
5.	**Discussion of ECV Raw Data Repository (S. Lockhart)** • A Raw Data Repository for ECVs will be created. – Raw data that has not been reviewed by the ECV working group will be housed on the ECV working group page in Workspace and will only be accessible by the working group. – The working group will meet on a quarterly basis to review all raw data. – ECV data that is deemed acceptable by the working group will be anonymized and posted on the AFST page on Workspace for review by the full subcommittee. – Suitable approved data will be compiled and posted on the AFST page on the CLSI website (communities) and will be accessible by any interested party. – The origin of data will be kept anonymous to all but members of the AFST ECV working group. • The M57 supplement will only contain ECVs for *Aspergillus* spp. and *Candida* spp. using the CLSI broth dilution methods. • ECVs obtained with other methods will be compiled separately (eg, Yeast One) and presented on CLSI website as well. • It was questioned if sequencing data should be provided. – It was agreed the some sequencing data may be needed for some moulds (eg, *Fusarium, Cunninghamella*). – Dr. Alexander indicated it is likely not necessary for common *Candida* and *Aspergillus* spp. (with the exception of *A. nidulans*, see Item 7) – Molecular identification data could also be made accessible for review on the CLSI website. • Dr. Procop (CAP) noted that providing guidance to the community on how to work with ECVs would be useful. • Ms. Cullen emphasized that is critical that reference data and commercial AFST data be kept separate.

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6.	**Analysis plan for ECV determination (Dr. Turnridge and Dr. Alexander)** • Dr. Alexander summarized the criteria for determination of ECVs: – Data from a minimum of three laboratories is needed. – No single laboratory is to provide more than 50% of the data. – Data submitted must be from a minimum of 100 unique isolates. – ECV will be determined using the iterative statistical method (Ecoff Finder – Dr. Turnridge). – Raw data will be reviewed/revised by the ECV Working Group prior to public release on CLSI website; the raw data will be available to AFST participants. – Incubation times will be those listed for specific organisms in M27 and M38. • Dr. Turnridge reviewed the methods for ECV determination (previously presented as a workshop at the 2013 annual meeting) that listed the pros and cons of the six major methods for determination of ECVs. – The "eyeball" methods (Kahlmeter) – The 95% rule (Pfaller) – The normalized resistance interpretation (Kronwall) – The iterative statistical method (Turnridge) – Multimodal analysis (Meletiadis) – Cluster Analysis (Canton) • Dr. Turnidge demonstrated the “Ecoff Finder" Excel calculation spreadsheet for ECV determination by the Iterative Statistical method. – Dr Turnridge gave a demonstration of how the " Ecoff Finder " is used to calculate ECVs. – The tool was distributed to participants as an Excel spreadsheet. – The “Ecoff Finder” tool for analyzing ECVs and the “Range Finder” tool for determining QC ranges are now accessible on the CLSI website.
7.	**Re-review of *Candida* and *Aspergillus* ECVs and specific issues (B. Alexander)** • Dr. Alexander reviewed the ECVs that were presented and/or were approved in January and May 2014. – Some discrepancies were noted between May and January votes on ECVs. – The AFST will postpone the re-vote on ECVs until all the data are recompiled and reviewed prior to public release on the CLSI website and publication in M57. – A threshold of 97.5% by the iterative statistical method will be used to determine all ECVs. • *Candida* ECV issues: – Are 95% statistical ECVs needed for Amphotericin B, Itraconazole and flucytosine (5FC)? No, the AFST decided that 97.5% statistical ECVs will be used for all species. – Are minimal inhibitory concentrations (MICs) for 97.5% statistical ECVs required for 5FC? Dr. Espinel-Ingroff will review the 5FC data. She also asked that anyone with available MIC data with 5FC for *C. glabrata* at the lower end of the range provided their data, as the available *C. glabrata/*5FC MICs were skewed toward the lower end of the testing range. **Item 7 (cont).**

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	• *Aspergillus nidulans* azole ECVs issues: – Trimodal distribution MICs observed for triazoles. – It was suggested that cryptic species of *Aspergillus* section Nidulantes have different MICs. – Re-evaluation of MICs with molecular identification by β-tubulin (*BenA*) gene sequencing may be needed (Dr. Lockhart). – It was requested that MIC data for all antifungals using (azoles, echinocandins and isavuconazole) with molecular identification be sent to Dr. Espinel-Ingroff. She will compile and review the data for ECV determination. Data from at least three laboratories and a total of > 100 isolates will be needed. • *Aspergillus fumigatus* and posaconazole ECVs (Dr J. Meis) – Dr. Meis presented MIC distribution data for azoles (posaconazole, itraconazole, voriconazole and isavuconazole) – All isolates were confirmed by molecular identification. – MIC data for *Aspergillus fumigatus* wild type (WT) vs resistant (*cyp51A* mutations TR_{34}, TR_{46}, G54C, G432C) – The data suggests that the selected ECV of 0.5 mg/mL is too high o It was found that majority of isolates with TR_{34-46} mutation in Cyp51A had an MIC of 0.5 mg/mL. o The current ECV would thus miss TR_{34-46} resistant isolates. • Dr. Espinel-Ingroff requested that any other non-reference method MIC data for *Candida* spp. be sent to her.
8.	**Planning and timing for review and vote on *Cryptococcus* ECVs was discussed**. • It was questioned if the vote should take place by April 2015 or postponed until January 2016. • Dr. Lockhart suggested that molecular identification may be necessary to define better ECVs for *Cryptococcus gattii/neoformans,* which is likely a complex of 6-7 cryptic species. • Thus, it was decided to postpone *Cryptococcus* ECV discussion and vote until January, 2016
9.	**Updates: Revision of M27 and M38 and development of M27/M44 and M38/M51 (Dr. Alexander)** • Timeline to publication: Submissions on hold until M57 is complete (see table on page 29, document 03A, and Item 3 above) – Ms. Cullen noted that it needs to be ensured that MIC data from multiple isolates from a single patient be excluded to prevent a bias. – Dr. Espinel-Ingroff indicated that it is specifically requested that one isolate per patient be submitted for ECV determination and that only data obtained by the CLSI broth microdilution method be included. – Dr. Lockhart pointed out that it would likely only be a problem for rare isolates, where sample size is small. • M38/51 Supplement content (Dr. Fuller, document 09A) – Dr. Fuller asked for clarification as what will be included in the M38/51 supplement. Currently there are no interpretive breakpoints for filamentous fungi and ECVs currently in M51-S will be included

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in M57-S.

- The AFST agreed that there will be very little data in the first version of the M38/51 supplement; however, new versions of the supplement could be published at least yearly or as new data becomes available (eg, isavuconazole breakpoints).
- It was decided that the M38/51 supplement will be published with QC data etc. and revised as interpretive breakpoints become available.

- **Siemens queries and points for clarification (Dr. Sei):** Dr. Sei submitted a series of questions for which she would like clarifications. Some of these points stem from discussion with the FDA related to Siemens activity as a device manufacturer.

Question 1 (section 7.2.2 and 7.8 in M27-A3): CLSI document is very prescriptive on how to dilute antifungal drugs for a small number of panels. It was suggested that it would be clearer if the end goal (the final concentration was provided).

- The voting members proposed that the language be clarified in next version of M27.
- It is important that the DMSO concentration be kept constant as the drug is diluted in the panel.

Question 2 (section 7.3 in M27-A3): Sabouraud dextrose (pH 5.6, glc 40 g/L) is different than modified Sabouraud / Emmons (pH 7.0, glc 20 g/L). Can both be used?

- Although it likely has no impact if either one is used, the only accepted media as indicated in M27-A3 is Sabouraud dextrose (pH 5.6, glucose 40 g/L).
- There is no data to support the use of the Emmons modification of Sabouraud dextrose media.
- The laboratory should only cultivate strains on Sabouraud dextrose when performing CLSI antifungal susceptibility testing according to the method described in M27.
- It was also noted that mentions of potato dextrose agar in M27 be deleted.

Question 3 (M27-S3 and S4): Will the antifungal subcommittee continue with setting breakpoints for Itraconazole? Not all the antifungal agents have breakpoints listed in S4. Nor is it clear if one should use S3 when no breakpoints are listed in S4. Should the laboratory report MICs with no interpretation when the current M27-S4 doesn't include interpretive criteria?

- Once a new supplement is published, the previous version becomes obsolete. Only the M27-S4 criteria are valid. Consequently, interpretive breakpoints that were provided in M27-S3 for itraconazole and 5FC are no longer valid and should not be used.
- Dr. Lockhart and Dr. Ghannoum indicated that the subcommittee plans to address these interpretation questions in a comprehensive review that could be published in JCM or CID. One article could address breakpoint interpretation and another ECVs after the publication of M57. It was noted that a webinar is also planned after the publication of M57. Dr. Castanheira also suggested that the College of American Pathologist mycology proficiency testing platform be involved in dissemination of the information.
- Ms. Hackenbrack noted that it should be specifically noted at the beginning of the supplement as to what has been revised since the previous edition was published.

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	Question 4 (M27-S3 and S4): Will the AFST continue with setting breakpoints for itraconazole and 5FC to be read at 24 hrs. Otherwise the panels still require incubation for 48 hrs. when all the other antifungals can be read at 24 hrs. – The M27-A3 methods still apply and a note allowing reading of azoles at 24 hrs. was included in the M27-S4. Therefore, itraconazole can be read at 24 hrs. According to M27-A3, 5FC must still be read at 48 hrs while all other antifungals can be read at 24 hrs. – Dr Lockhart indicated that at a previous AFST meeting, use of 24 hrs reading for 5FC had previously been shown to be equivalent to 48 hrs reading. However, this information was not integrated into M27-S4. As 5FC is typically not reported for *Candida* spp., it should not prevent laboratories from performing most readings at 24 hrs.
10.	**Caspofungin working group update (D. Perlin)** • Dr Perlin provided a review of echinocandin resistance mechanisms and caspofungin interlaboratory variation seen with CLSI broth microdilution method. – Whereas multiple targets and mechanisms are involved in antifungal resistance to azoles, resistance to echinocandins occurs through a single mechanism: mutations in FKS1/2 glucan synthase gene. Mutations that confer resistance to echinocandins are well defined and generally restricted to two hotspot regions (see Arendrup and Perlin, Curr Opin Infect Dis. 2014; 27(6):484-92). – Unacceptable variation in MICs has been reported with caspofungin with both the EUCAST and CLSI microdilution methods (Espinel-Ingroff, AAC 2013 57:5836; Arendrup, AAC 2011). o EUCAST has decided to abstain reporting to caspofungin MICs. o The new breakpoints in M27-S4 led to false reporting of resistance for *C. glabrata* and *C. albicans* (major errors) in some laboratories. o Present QC strains are insensitive to variation that may affect the lower end of MIC distribution; therefore, better QC strains are needed. – Multiple factors have been proposed to explain variation: stability of reagents, plastic binding, use of DMSO, and endpoint reading. The use of Tween has been suggested to reduce caspofungin adherence problems. – Pfaller et al. (JCM 2014, 52 1: 108:114) showed that both anidulafungin and micafungin were found to provide more reproducible MIC results than caspofungin with 90.9 and 96% concordance, respectively. – A review of reference broth microdilution vs other commercial methods points to a lot to lot variability with these methods as well. The interlaboratory variation for caspofungin impacts commercial and reference methods. – The following questions were also submitted to the AFST: o Are anidulafungin and micafungin suitable surrogate markers for caspofungin susceptibility? o Should molecular testing for echinocandin resistance become the gold standard? • **Project proposed from the Caspofungin Working group (M. Castanheira, document 10)** This project would: – Identify new QC isolates to monitor echinocandin susceptibility (which can detect loss of susceptibility in low range MICs). o Phase I: Detect potential QC isolates that detect loss of potency for echinocandins by the

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	incremental dilution MIC method (100%, 85%, 50% strength). o Phase II: Assess reproducibility of MIC results using GMP prepared panels. – Sort through variables impacting caspofungin testing. o Phase III: Assess the variables of panel preparation that affect caspofungin CLSI broth microdilution method. o Reagents (96 well plates, RPMI broth and echinocandin) would be provided to participating labs. – Dr Ramy (FDA) asked the AFST to provide guidance on the interlaboratory variation issues observed with caspofungin. o Dr Alexander proposed that the AFST send a memo to clinicians to explain the current issues with caspofungin AFST. o M. Hackenbrack will determine how this might be done. – It was also suggested that a detailed questionnaire be sent to evaluate the methodological issues that may be responsible for the interlaboratory variation (eg, 96 well plates that are used). – Overall, the proposal was well received; however, it was unclear as how this project could be financed to avoid conflict of interest with drug manufacturers.
11.	**Tier 3 QC data review (S. Cullen)** • Ms. Cullen reviewed the latest Tier 3 QC data with *C. parapsilosis* and *C. krusei* QC strains with different antifungal drugs. – For this round, she requested that laboratories provide information on the diluent used (DMSO vs water) and if treated or untreated 96 well polystyrene plates were used. Only three laboratories provided new data. – In the data gathered, no shift was seen with untreated 96 well plates. – Current ranges appear acceptable for all antifungal drugs. Revision is not required. – Dr. Lockhart noted that the mode of *C. krusei* QC strain (ATCC 6258) for caspofungin is 1 mg/mL which would classify the strain as resistant when it is known to be susceptible. It was suggested that the range may not be adequate for this QC strain. • The AFST was in favor of repeating QC data review every 2 years. Ms. Cullen and the AFST requested that more laboratories submit data.
12.	**Isavuconazole interpretive breakpoints for *Aspergillus* spp. (L. Kovanda)** • Ms. Kovanda (Astellas) presented an overview of clinical and animal studies performed with isavuconazole that support new interpretive breakpoints for Aspergillus spp. – The goal pursued was to seek input from the AFST. Astellas is not currently seeking approval of the proposed breakpoints for *Aspergillus fumigatus.* Astellas will complete their New Drug Application and then will request formal approval from the AFST after receiving input from the FDA. – Isavuconazole is seeking approval for the treatment of invasive Aspergillosis and Mucormycosis (Orphan status and QIDP designation granted by FDA). – Clinical trial results (510 patients enrolled in the studies) demonstrated the non-inferior efficacy of isavuconazole vs voriconazole for treatment of invasive Aspergillosis. Outcome response success rate found to be equivalent to voriconazole (approx. 35%). – ECVs and MIC distributions for relevant *Aspergillus* spp. were presented with proposed ECVs from AFST subcommittee January 2014 meeting.

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Item 12 (cont).

Species complex or section	No. of isolates / No. laboratories	Modal MIC	Statistical ECV 97.5%
Aspergillus fumigatus	855 / 8	0.5 mg/L	1
Aspergillus flavus	444 /7	0.5 mg/L	1
Aspergillus nidulans	106 / 3	0.125 mg/L	0.25
Aspergillus niger	207 /6	1 mg/L	4
Aspergillus terreus	384 / 4	0.25 mg/L	1

- Three pharmacodynamic models model were used to assess PK/PD with *A. fumigatus*.
  - Invasive pulmonary aspergillosis in neutropenic murine model
  - Invasive aspergillosis in a non-neutropenic mouse model.
  - Dynamic *in vitro* model of human alveolus.
- In all models, efficacy was seen in isolates with MICs up to 2 mg/L, regardless of presence of absence of *CYP51A* mutants.
- *In vitro* activity of isavuconazole against resistant (*CYP51A*) *A. fumigatus* demonstrate that the outcome in mutant strains is largely concordant with MICs not the presence/absence of specific mutations.
- Exposure response and outcome by MIC analyses in phase 3 clinical studies were shown for *Aspergillus* spp. Favorable outcome observed for isolates with MICs ≤ 4 mg/L.
- Proposed interpretive criteria for *A. fumigatus* were the following and received favorably by the AFST.

Organism	Susceptible	Intermediate	Resistant
Aspergillus fumigatus	≤ 1 mg/L	2 mg/L	≥4 mg/L

- Dr. Ghannoum commented that the data might support an intermediate range from 2-4 mg/L and a resistant breakpoint of >4 mg/L.

A formal vote will take place once Astellas has completed NDA review.

13. **Next meeting**: Web conference – April 2015; Annual meeting – Saturday, 9 January 2016 in Tempe, Arizona

ACTION ITEMS			
No.	**Description**	**Responsibility**	**Due Date**
1	Complete draft of M57	ECV working group	February 2015
2	Complete Draft of M57-S	ECV working group	May 2015
3	Complete draft of M27-A4	S. Lockhart L. Kovanda	May 2015
4	Complete draft of M27/M44 new supplement	B. Alexander A. Fothergill	May 2015
5	Complete draft of M38-A3	Ana Espinel-Ingroff P. Dufresne	May 2015
6	Complete draft of M38/M51 supplement	J. Fuller M. Ghannoum	May 2015
7	Create repository for ECVs on CLSI website and review data	ECV working group Ms. Hackenbrack	In progress
8	Distribute "Ecoff finder" to CLSI community	J. Turnridge	Completed
9	Send 5FC *C. glabrata* MIC data (low range) to Dr. Espinel-Ingroff	All	February 2015
10	Send MIC data for molecular identified *A. nidulans* to Dr. Espinel-Ingroff (all antifungals)	All	February 2015
11	Send Yeast One method to Dr. Espinel-Ingroff (all antifungals)	All	February 2015