FTS-CDC-EPO

January 26, 2006
2:00 p.m. CST

Coordinator — Speaker, Ms. Denise Koreniowski. Thank you, ma'am. Please begin.

D. Koreniowski — Thank you. Good afternoon. This is Denise Koreniowski, training associate, speaking to you from the National Laboratory Training Network, Boston office; located in the State Laboratory Institute in Boston, Massachusetts. Welcome to our teleconference: "What's new in the 2006 Standard for Antimicrobial Susceptibility Testing? New Recommendations from the Clinical and Laboratory Standards Institute." Financial support for this program is generously provided by Ortho-McNeil Pharmaceuticals.

Before we begin the program, a few notes. CDC, our planners and our presenters wish to disclose they have no financial interest or relationships with the manufacturers of commercial products, suppliers of commercial

services or commercial supporters with the exception of Janet Hindler. She wishes to disclose she is on the speaker's bureau of Ortho-McNeil Pharmaceuticals … Microscan.

This presentation will not include any discussions of the unlabeled use of a product or a product under investigational use. Also, after the program, each participant needs to register and complete an evaluation form. Documenting your participation helps us to continue to bring high-quality training programs in a variety of formats. To do this, go to www.cdc.gov/phtnonline. The course verification code is 2006. Again, the Internet address is www.cdc.gov/phtnonline. The verification code is 2006.

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can only hear us. If you experience any problems with the line during the conference, press star zero. This will signal the attendant that you are having a problem. If the program experiences technical difficulties, please do not hang up. Stay on the line until the issue is resolved.

Again, welcome and thank you for joining us. We have over 450 sites from across the United States and also sites in Canada, New Zealand and Spain listening to this teleconference. Today's speaker is Janet Hindler, who speaks to us from UCLA Medical Center in Los Angeles, California. Janet Hindler is a Senior Specialist in Clinical Microbiology for the Division of Laboratory Medicine at UCLA Medical Center in Los Angeles, California. She is working as a consultant with ATHL to develop and conduct training on antimicrobial susceptibility testing. It is my pleasure to introduce to you and to welcome our speaker, Janet Hindler.

J. Hindler Hello and thank you, Denise, for that introduction and thank you to all of you out there for joining in to our third annual audio conference to provide you with an update of the current Clinical and Laboratory Standards Institute standards for antimicrobial susceptibility testing.

Now if you'll go to slide two, you will see the objectives for today's presentation. Hopefully by the end of this program, you will be able to outline the major changes found in the new CLIS tables, the M100-S16 and the standards for distafusion, the M2-A9 and MIC testing, M7-A7. Also, you should be able to discuss how to optimally use the new distafusion and MIC quality control troubleshooting guide and finally, you should be able to describe a strategy for implementing the new practice guidelines in your laboratory as appropriate.

Now if you'll go to slide three, this is a listing of the primary standards that we're going to discuss today - those that were recently published by the Clinical and Laboratory Standards Institute. First the table, the M100-S16 version. These became available earlier this month. As most of you know, the tables that contain the recommendations for testing and reporting, the breakpoints and the quality control ranges are updated every year in January. These tables are to be used with the text documents to describe how to perform the test, the distafusion test. The current document is the M2-A9. The document for MIC testing is the M7-A7. These are brand new documents.

As many of you know as well, these documents are updated every three

years. 2006 was part of the three-year cycle. So now we have new recommendations or new standards for guiding us for distafusion and MIC testing. For those of you that are doing testing in your laboratories, it would be helpful to have all of these new documents in your laboratories.

As part of the information that we provided for you either on the CD-ROM or the Web site, there is a link; there is information to CLSI that will help you determine how you can procure these for your laboratory if you do not already have them.

Now if you go to slide four please, I just want to list some of the reference terminology that I'm going to be using throughout this presentation. So when I refer to M100, this means the new tables - the M100-S16. When I talk about the M2, this means the new distafusion document - the M2-A9. The M7 refers to the new MIC document- the M7-A7. And the M45; we're going to talk briefly about a new document, a new guideline that has recently been published by CLSI that describes how to test fastidious organisms or infrequently countered organisms. Finally, when I talk about CLSI or the Clinical and Laboratory Standards Institute, I think all of you are aware that this organization was previously known as the NCCLS.

Now if you go to the next slide please, I just want to review the information that is contained in the CLSI M100 table. If you started about 8:00, you will see an indication that there is a listing in M100 that includes the updates in this particular edition. If you go to the next little circle, you will see that this section of M100 contains the tables for distafusion testing. This includes the set of tables that describe which drugs to test and report, the breakpoints or the interpretative criteria, various quality control tables and there is some additional information as well.

Then you go into the next section of M100 and there you will find all the tables that relate to MIC testing or the M7 document. Again, too, you will see the MIC recommendations for drugs for testing and reporting, the breakpoints or the interpretative criteria, the quality control ranges and there are a few other tables as well.

At the back portion of the M100 booklet, there's a glossary. This contains the listings of the various drugs and drug classes and subclasses and the actual agents that are in each of the different classes and subclasses. Finally at the end of the table, there is a section that includes questions that have been submitted to CLSI related to the susceptibility testing documents and the answers that have been provided by the Antimicrobial

Susceptibility Testing Subcommittee.

Now this year, since it was a year when both the M2 and the M7 were also updated, you will find the questions and answers this year in the back of M2 and M7. On alternate years, these questions and answers will be in the M100 document. Some of you who have gotten your documents, gotten your M100 realize that you probably got some tabs or stickers with your tables. This was CLSI's response to some of you that asked for an easier way to separate the different tables. You could add those to your tables either all of them or a few of them and hopefully the intent here is to help you better find the information that you're looking for.

I might mention too there are other options to obtaining these tables other than in a print version. You could find more information related to this on the CLSI.org Web site or actually contacting someone at CLSI.

Now let's go to slide six please. This is just a snapshot of the page that lists the updated information in M100-S16. Basically, this guides all of the changes that have occurred since the publication of M100-S15. This will include a summary of the material that we're covering in today's teleconference.

I might also mention that as part of the material that we provided for this teleconference, we have actually also included a checklist. You might want to refer to that checklist when you're decided which of these changes to implement in your particular laboratory. It's just a slightly different presentation that lists all of the changes and points for you to consider when you're decided what types of changes need to be made in your particular laboratory.

Now let's please go to slide seven and let's start talking about some of these changes in the M100-S16. If you'll turn to slide eight, here is another snapshot. This time, this is a snapshot of a box and I'll refer to this as "the box" in the beginning portion of the M100-S16 table. This box has been expanded from a box that was in the previous documents. Basically, this describes how the text recommendations and the CLSI standards compare to test recommendations provided by commercial manufacturers of commercial diagnostic susceptibility testing devices.

The beginning part of the information in the box has really not changed that much. However, the expansion includes more information on the SI&R breakpoints and there's some supplemental information that

describes and explains why the CLSI breakpoints in some cases may differ from the breakpoints provided by regulatory agencies. Again too, we're going to talk about some of these changes today and explain this to you so you could have a better understanding when you see some of this information in the M100 standards and may hear about some of this from your diagnostic manufacturers.

So let's go on to slide nine and again, to recap a little bit more of what's in the box. As I mentioned, the box contains a description of what is in the M100 standard. Basically, it mentions that the M2, M7 and M100 describe standard consensus reference methods. It also goes on to say that the United States Clinical Lab can use the CLSI test method as written.

So for example, if you're performing the distafusion test, you're probably following the recommendations in M2 as they're written. You also have the option of using a method that performs comparably to the CLSI reference methods. If you're using an FDA cleared diagnostic susceptibility testing device, you are using a product that does perform comparably to the CLSI reference method. Here in the little box, I'm just defining-- We talked about a diagnostic AST device. We're talking about a commercial instrument or other type of test used to determined

antimicrobial susceptibility in Vitro.

Now if you go to the next slide, and this slide is a little bit busy. I might mention on your CD-ROM and also on the Web site you could find an 8.5 x 11 inch version of this particular flow diagram if you want to look at it more closely. Basically, we've provided this to help explain some of the new information related to breakpoints and clinical indications because there is new verbiage in M100-16 that refers to both of these concepts, to the breakpoints, FDA breakpoints versus CLSI breakpoints and there's also some expanded information about recommending drugs for test and report with FDA approved clinical indications.

So let me take you through this little flow diagram on page ten. Basically, what this is is how we take a new antimicrobial agent through the series of getting it approved. So we're describing this as the new antimicrobial agent pathway. The first thing that happens is the pharmaceutical company does extensive studies, collects extensive data to prove that their drug warrants consideration for FDA approval. They put all of this information today in what's called an NDA or a New Drug Approval packet and they submit this to the FDA.

Well, some of the information contained in that packet includes clinical outcome data from using that drug, microbiological data that shows how that antimicrobial agent acts against various organisms in Vitro, proposals for breakpoints - SI&R breakpoints - proposals for quality control ranges and there are lots of other additional information in that request packet. FDA analyzes all of that information. If FDA approves what's been submitted, the company will then go back and produce their product labeling. In this product labeling there will be therapeutic details and also FDA breakpoints. So here this is the package insert or the product labeling that accompanies the drug that will be used for patient administration.

I might mention too; if you look at the little green box on the left under that first part of the flow diagram, I have mentioned here that the testing to establish the FDA breakpoints is performed using the CLSI standard reference methods. Now if you go over to the right-hand side of the flow diagram, you will see that at the same time or around the same time, the company may submit a condensed version of the NDA request packet to the CLSI. This, again, will include clinical outcome data. It may not be quite as extensive as what they submit to the FDA. They will also provide microbiological data, ask for certain breakpoints, quality control ranges

and there is some other information in this packet as well.

The CLSI subcommittee on antimicrobial susceptibility testing reviews this information and if they approve it, the testing details and the CLSI breakpoints will be provided in the laboratory testing reference standards. Here we're talking about the M2, the M7 and M100.

Now if you look at the center portion of this pathway, you will see what happens with a diagnostic manufacturer. The diagnostic manufacturer, in order to get a new drug approved on their panels, has to submit substantial information to the FDA. Basically this is considered performance data. In the little box on the right, I've got that the diagnostic AST device performance data is based on the manufacturer showing or demonstrating that their device will produce results that are comparable to the results that are produced with the CLSI standard reference method.

If the FDA approves this information that is submitted by the diagnostic manufacturer then this is cleared. That particular drug is cleared for testing on that particular manufacturer's panel and then the testing details are provided in the diagnostic AST device product labeling. By law, the diagnostic manufacturers are required to include the FDA breakpoints. So

again here too, once a diagnostic product is FDA cleared basically what we're saying is that the results that are generated by that commercial product should be comparable to those results generated by the CLSI reference method.

Now let's go on to the next slide and we'll talk about a few points related to FDA versus CLSI breakpoints. They nearly always agree. So usually the breakpoints in the FDA product labeling for the therapeutic drug is identical to those published in the CLSI M100 table. However, sometimes there is disagreement. Sometimes, there are only FDA breakpoints. A current example would be that for Tigecycline. Some of you are being asked to test this drug in your laboratory. You will note that there are no breakpoints for Tigecycline in the CLSI tables. If you were to test this drug in your laboratory, you would have to resort to the FDA breakpoints found in the therapeutic product labeling.

Sometimes, there are only CLSI breakpoints and this might be before the drug is FDA cleared or if the drug is used in other countries. The CLSI standards are now global standards. There may be some drugs that are prescribed in other countries that are not available in the U.S. So you may see some breakpoints for these drugs in the M100 table.

Now sometimes, the breakpoints are modified by CLSI. This is something that has occurred this year with the story related to Vancomycin and Staph aureus and I'm going to cover this in some detail.

Now if you go to slide 12 please, this just shows you the CLSI versus the FDA breakpoints currently available for Vancomycin and Staph aureus. So for CLSI, the new breakpoints for SI&R less or equal to two micrograms per ML for X, four to eight is intermida, and an MIC at greater than or equal to 16 would be interpreted resistant. The FDA has not made a change in the breakpoints for Vancomycin and Staph aureus. So basically, those are now different from those in the CLSI M100-S16 document. Again, I want to reiterate that the diagnostic manufacturers, by law, must use the FDA breakpoints.

Now in the little box on the bottom of slide 12, I've indicated some additional information that's found in the box in the beginning of M100 that states that a clinical laboratory can use CLSI or FDA breakpoints. But then there is that caveat that if you're using a commercial AST device, the system must use the FDA breakpoints. If you were to use the CLSI breakpoints or breakpoints other than those specified in the diagnostic

manufacturer package insert, you would be using that product off label. Therefore, you would have to validate it if you use anything different other than what's specifically stated in that diagnostic product package labeling. It would not be easy for you to do that type of validation.

Now let's go on to slide 13. We'll talk about another change or another clarification that was introduced this year. Now this is an excerpt from the introduction to the tables in M100-S16. Basically, it describes what is contained in the table. If you look at item one here, you will see it talks about tables one and 1(a) that describes the suggested grouping of antimicrobial agents that should be considered for routing testing and reporting by clinical microbiology laboratories. Now the sentence is in boldface type. I think a lot of you know that the changes in M100 do appear in boldface type and this is another way you could identify changes that had occurred since the last publication of the tables.

If you go to slide 14, you will see a larger font version or a larger print version of that next sentence. Basically what that says and it's excerpted right out of the previous page, slide 13: "And these guidelines are based on drugs with clinical indications approved by the Food and Drug Administration in the United States." So the change here is the addition of

that terminology "with clinical indications approved by the FDA." In other countries, placement in tables one and 1(a) of antimicrobial agents should be based on available drugs approved for clinical use by relevant regulatory agencies.

Now let's go on to the next slide. I think it's important for all us to understand what we mean by these FDA approved clinical indications and where do we find that information? So what I have decided to do is take you through the product labeling for a therapeutic agent. I've selected Daptomycin. I might mention none of us involved with this program had any relationship with the manufacturer of this drug. I selected this particular drug because the labeling is relatively new and it does well describe the concepts I'd like to share with you today.

So this actually is the drug labeling or the package insert that accompanies Daptomycin, which is also known by the trade name of CUBICIN, manufactured by Cubist Pharmaceuticals. If you wanted to see this package insert in its entirety, I've given you the link to the Web site where you can locate that.

Now let's go on to the next slide. What is this drug product labeling or

package insert include? Well it has many sections and it includes indications, basically clinical indications, and usage sections. The information here is based on demonstrated clinical efficacy. They take into consideration in Vitro susceptibility test data and also clinical outcome data.

There's another section that describes microbiological activity in Vitro. The information here-- When organisms are listed to have microbiological activity, this doesn't necessarily mean that that drug is going to have clinical efficacy against those organisms. The information in the product labeling provides substantial data for clinicians, pharmacists, diagnostic susceptibility test manufacturers, patients, … microbiologists and others. So there's a wealth of information in this product labeling that can benefit a lot of healthcare professionals as well as the patient who might be taking that drug.

Now let's go on to slide 17 please, and look at the definition of clinical indication. What does this actually mean when we say, "That drug has a clinical indication?" We could describe a clinical indication as a disease entity that has a specific set of signs, symptoms and laboratory findings that can be described to clinicians in that product labeling. If we go back

to our example of Daptomycin, Daptomycin has a clinical indication for complicated skin and skin structure infections. This is spelled out in that product label.

What this means is that Daptomycin can be used to treat Staph aureus, including MRSA wound infections as noted in the package insert or the product label. Generally or almost always, the clinical indication is linked to specific pathogens. Now what we're saying is that even though there's information in that indication section for certain drugs, organisms and infections, it doesn't necessarily mean that this drug may not work for other infections but there was insufficient data to get those included in the indications section when the drug was submitted to the FDA.

Now let's go on to slide 18, and this is a snapshot from the indications and usage section from the Daptomycin product label. You can see at the top of this slide right here it says that Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following: Gram-positive organisms, including Staph aureus, the methasone resistant isolates and it goes on and on and on to talk about other organisms for which there has been defined clinical indications. There's some other information in here as well that talks

about how to use the agent.

Now let's go on to the next slide, slide 19 please and this is a snapshot from the microbiology portion of that product label. Here you can see that the first part here reiterates those organisms that have been shown to be effectively treated with Daptomycin, not only showing activity in Vitro but also clinical outcomes. It refers back to the indications and usage section.

So here it says, "Daptomycin has been shown to be active against most isolates of the following organism both in Vitro and in clinical infections as described in the indications and usage section." Now if you see below that pink line, it talks about those organisms for which Daptomycin has shown in Vitro activity only. This is proceeded by the description, "The following in Vitro data are available but their clinical significance is unknown. Greater than 90% of the following organisms demonstrate an in Vitro MIC less than or equal to the susceptible break point for Daptomycin versus the bacterial…. The efficacy of Daptomycin in treating clinical infections due to these organisms has not been established in adequate and well controlled clinical trials."

So the drug has … but there was insufficient clinical data to show that Daptomycin will be effective in treating infections caused by these organisms. It's not necessarily saying that it's not going to work, but there was insufficient clinical data to get these organisms put in the clinical indications section.

Now let's go on to the next side and this is just a snapshot of some additional information in that product label. Here are the breakpoints or the susceptibility interpretive criteria. As you can see, there are MIC interpretive criteria as well as distafusion interpretative criteria. Currently, the MIC interpretative criteria for Daptomycin in the FDA product labeling is identical to those in the CLSI M100 table. I might mention too, and I'll refer to it a little bit later, that CLSI did eliminate distafusion breakpoints for Daptomycin and I'll explain a little bit more about that when we get to the changes for gram-positive organisms.

Now let's go on to the next slide. All of this clinical indication information is reflected in the modified title for table one where you now see the label is, "Suggesting Groupings of Antimicrobial Agents with FDA Clinical Indications." That's a new term. This wasn't in the M100-S15 table one. Again, it should be considered through routine testing and

reporting. This is the one for non-fastidious organisms. So here too, this goes back to the clinical indication as listed in that product label. So hopefully, you have a better understanding of what we mean and why we introduce that clinical indication terminology.

Well let's go on to slide 22 and talk a little bit about why we might see some drugs listed in table two with breakpoints or interpretative criteria, but these are not listed in table one. At the top of the slide, you can see a snapshot of the top of that table one that I just showed you. At the bottom, the corresponding breakpoints for the non-Enterobacteraceae. Just so you get an idea … we talked about table two. We're talking now about the break point table.

If you go to slide 23, I just listed a list of possible reasons why the drug may be included for breakpoints in table two but not listed as a suggested drug for routine testing and reporting in table one. Well, if a drug does not have an FDA clinical indication for that organism, it's not going to appear in table one but might still have a break point in table two. The drug may not be used in the United States. As I mentioned earlier, there are some drugs that are only used outside of the United States. The drug may not be a first choice or alternative drug suggested for routine testing for the

organism. An example would be Pipercillin/Tazobactam and Pseudomonas aeruginosa. There are breakpoints for this drug combination, but this is not included in table one since it's not considered a first choice alternative drug for treating Pseudomonas aeruginosa infections.

Now let's just shift gears a little bit and go on to slide 24. Some other changes that have occurred in 2006 involves the slight modification of the definitions of SI&R. I've included the new definition and also the old definition on the bottom of these slides. Let's just review what that new definition is and basically, some of these involve just rewording to be more comprehensive in what the intent of this categorization may be.

So for susceptible, this implies that "Isolates are inhibited by the usually achievable concentration of antimicrobial agent when the recommended dosage is use for the site of the infection." Basically, the change here has been that the term "appropriately treated" has been eliminated from this definition, but still the overall intent is still quite the same.

Let's go on to slide 25 where there's only been a very slight modification of this definition. So on slide 25, we talk about the intermida category and

the definition here is that "The intermida category includes isolates with antimicrobial agent MICs that … usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates." The intermida category implies clinical efficacy in body sites where the drugs are physiologically concentrated. For example, the … and beta-lactams in urine where you get higher concentrations or when a higher than normal dosage of drug can be used. For example, the beta-lactams.

Again, this category also includes a buffer zone, which should prevent small uncontrolled technical factors from causing major discrepancies in interpretation especially for drugs with narrow pharmaco-toxicity margins.

If you go to slide 26, there's been a slight clarification of the definition of "resistance." There's really no difference in the intent. Now the current wording is that "Resistance implies that the isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range where specific microbial resistance mechanisms as likely, such as beta-lactomases and clinical efficacy of that agent against the isolate has not been reliably shown in treatment studies." So again, two very minor changes in these definitions of SI&R.

Now let's go on to slide 27 please. Here, I'm going to review the definition and the slight modification here when we have a drug bug combination for which there was only susceptible break point. There's no intermida or resistant break point.

Basically, what this means is that if there's only a susceptible criteria or susceptible break point, and for some organism antimicrobial combinations, the actions, and we've added or rare occurrence of resistant strains, precludes defining any result categories other than susceptible. For strains yielding results suggestive of a non-susceptible category, organism identification and antimicrobial susceptibility test results should be confirmed. Subsequently, the isolate should be saved and submitted to a reference lab that will confirm the results using a CLSI reference dilution method. This is found in the introduction to the tables in a little box.

Now let's go on to slide 28 and what do we mean by "actions" versus "rare occurrence?" How do we know if there's ever been a non-susceptible isolate for those drug bug combinations where we have only susceptible breakpoints? Now we can check the CLSI, M100-S16 tables

that contain the suggestions for verification of susceptibility results and confirmation of organism identification. This is actually table four in the M2 section of the tables or table eight in the M7 section of the tables.

If you go to slide 29, I've just included a slight excerpt from one of those tables and they're basically identical in the disk and the MIC portion of M100. Here too, you will see the title: "Suggestions for verification of susceptibility results and confirmation of organism identification."

So here you can see, for example, we've listed for Staph aureus that category one contains those drugs that should be verified when certain results are obtained. So all labs should verify, for example, a Linezolid non-susceptible Staph aureus because we only have susceptible interpretive criteria for Linezolid for Staph aureus.

Now if you look under Streptococcus pneumoniae, we're also saying that all labs should verify Vancomycin non-susceptible Streptococcus pneumoniae because there's only a susceptible break point for Vancomycin in Streptococcus Pneumoniae. The difference between the presentation of Linezolid for Staph aureus and Vancomycin for pneumococcus is that when you look at the Vancomycin in

pneumococcus, you see that little superscript C and that does have an implication. What that means is that if you see that superscript C, Vancomycin non-susceptible pneumococcus have never been documented in the literature. In contrast, for Linezolid and Staph aureus, rarely has there been Linezolid non-susceptible Staph aureus.

So let's look at this little bit closer. If we look at the pneumococcus and Vancomycin in slide 30, you will see that I've reprinted the MIC breakpoints where there's only a Vanco susceptible break point, no intermediate or resistant break point since intermida or resistant strains or strains other than susceptible have never been encountered. So we wouldn't know how to describe one or identify one that was either intermedia or resistant.

The protocol that laboratories should follow; if you were to find, for example, a Vancomycin MIC that was other than one or less for pneumococcus; so let's say you've got a Vancomycin MIC of eight for pneumococcus. What would be the protocol? You investigate this by repeating the identification. Make sure this wasn't some other gram-positive that had intrinsic Vancomycin … such as Pediacoccus or Lactobacillus, confirm the susceptibility test to make sure it reproduces

and in some cases, you might want to use an alternative method. By all means, save the isolates. Send it to a reference lab. They can test this organism by a CLSI MIC reference method.

Here too, this is very, very important because those of us in clinical laboratories are on the first line of identifying emerging resistance and its our public health responsibility to make sure we inform the appropriate individuals if we were to encounter something that's never been reported that particularly can have some public health significance. So it's our obligation to pursue these and not just to let them ride. We have to save the isolate because nobody is going to believe we have one of these unless they can be confirmed by very reputable laboratories that do this all the time.

So here too, because this Vancomycin with pneumococcus had that superscript C, what that meant again was that Vancomycin non-susceptible pneumococcus had never been documented.

If you go to slide 31, similarly, for Staph aureus/Linezolid we only had susceptible breakpoints. But here, the presentation of that in the verification table, there was no superscript C. So what we're saying here

is that Linezolid non-susceptible Staph has been reported on rare occasions. Nevertheless, the protocol would be for laboratories to verify this if they were to find a Linezolid result that was other than four or less for Staph aureus because it's been very rare that these have been reported and you'd want to make sure that there wasn't some technical problem or some misidentification of the organism, reproducible results for this particular unusual observation.

So hopefully you can appreciate how we could identify those isolates where we've never seen resistance or resistance may have been reported on rare occasions. As most of you know, the more these drugs are used, the more likely we are to see the occurrence of non-susceptible results.

Now let's go on to the next slide and shift gears a little bit. This is just a snapshot from the introduction to the tables again, in that section labeled "Warning," which describes those comments related to organisms where there may be activity of certain drugs but these drugs are not clinically effective even though there's a susceptible result in Vitro. This is basically just an editorial change where we've included to that list the ESBL producing Klebsiella, E. coli, and Proteus mirabills; again, reminding everyone that the penicillins, … and … may appear active

against these ESBL producing strains in Vitro but they're clinically ineffective and should not be reported as susceptible. So this is really no change in testing. This is just really an editorial change where we've added this particular group of organisms and drugs to the list.

Now let's go on to slide 33. Another minor change has been the clarification of the incubation temperature range for the reference of distafusion and MIC tests. That range is now 35-plus or minus two degree centigrade with the exception of tests for Staphylococci as I've shown on this side right here and also for Neisseria gonorrhea. For Staphylococcus, we're saying if you're using one of the CLSI reference methods that detects for 35-plus or minus two degrees; however, a notation is made that testing at temperature above 35 degrees may not detect all methicillin-resistant Staphylococci.

So if you're doing a reference method and you're incubating these in an offline incubator, you would want to set that incubator at temperatures to go no higher than 35 degrees when you're doing tests to detect methicillin-resistant Staph, which might be your distafusion test with Cefoxitin or your MIC methods with Oxacillin or whatever. Just a reminder again; if you are using a commercial product, you have to follow that

manufacturer's recommendation. If they say to incubate at alternate temperatures, that is what was FDA approved to demonstrate comparable results to the CLSI reference method. So you always follow what's in that package insert, even if it's different from what's recommended in the CLSI document.

Okay. Let's go on to slide 34, and we'll talk about new guidelines that were very recently published by CLSI as a proposed guideline. The title of this is "Methods for Antimicrobial Dilution and … Susceptibility Testing on Infrequently Isolated or Fastidious Bacteria." This was published for the first time back in October. It is available from CLSI and let's talk just very briefly about this particular new guideline.

Well if we go to slide 35, what I want to emphasize here is that this document in contrast to M7 and M100 is referred to as a guideline in contrast to M2, M7 and M100 as referred to as standards. When we talk about a CLSI standard that's the highest level of document and if you're going to be following that, you should be using it in the unmodified form.

The next level would be a guideline. When you're using these documents as a guideline, there's more opportunity to modified these. Basically,

some of the data that goes into a guideline is not quite as robust as that which goes into a standard. Now M45 is based upon data in the published literature, extensive review of the literature; it's based on MIC distributions and resistant mechanisms of organisms for generating the breakpoints and in contrast to some of the data that goes into the M100, there was very limited clinical data available to support some of the decisions because some of the organisms included in this document are very infrequently encountered and there's not as much data available for this.

M100, again, is a standard and it's based on substantial clinical data in addition to in Vitro data. For those of you that are interested in determining what kinds of data, go into the break point decisions and quality control decisions. For the information that's ultimately published in M100, there is another CLSI document - M23 - that describes exactly what is required to get a break point or quality control range into the M100 tables.

The other thing I might want to mention is that the "P" represents, this is the proposed guideline at this time and that's for the first time that is presented, it's usually at the proposed level. It will likely become an

approved level guideline in the near future.

If you go to slide 36, I just want to show for those of you that are interested in getting more information on what these definitions area - standard, guideline, proposed, approved - on the inside of the cover of all of the CLSI documents, there are the subscriptions. So if you care to learn any more about that, you could go to the inside cover of M2, M7 or M100.

Now let's go on to slide 37. This is just a listing of those organisms that are included in the M45 guideline for infrequently isolated or fastidious bacteria. For all of these, there are breakpoints and for … Pasteurella and … there are some distafusion breakpoints as well.

You might notice here too on this particular listing there is a listing at the bottom of the first column for the … group and the "H" here refers to the Haemophilus. Some of you realize that there are guidelines for Haemophilus in the M100 document. However, here the … organism, the Haemophilus here pertain to the more unusual Haemophilus organisms such as the … group.

If you go to slide 38, this is just an excerpt from the description of what's

contained in the M45 guideline. This is a statement right out of that guideline. What it states is that "Testing should only be undertaken in consultation with infectious diseases or other expert physicians that can assist in determining if susceptibility testing is needed in the management of a specific patient."

Now what this is saying here is that the infections caused by these organisms are frequently treated empirically and it may not be essentially to do susceptibility testing on them. That's why we suggest that if you're going to be doing susceptibility testing, if you're asked to do susceptibility testing on these organism to suggest to the clinician that they should make sure they consult about this particular organism and infection with an infectious disease person who make sure the susceptibility testing information really can enhance information that goes into the therapy decision and patient management decisions.

Okay. Let's go to on to slide 39. This is just a snapshot of one of the tables in M45P, that Coriny bacterium species where we only have MIC breakpoints. At the top of this slide, you will see that there's a little box that describes testing conditions for the Coriny bacterium, minimal quality control recommendations and agents to consider for primary testing.

There are also some general comments.

If you go to the next slide, you will see some additional information on the bottom of this table that talks about some resistant factors related to the … bacteria where is says "Some species of Coriny may exhibit resistance to multiple drug classes." It also has a little section, "Reasons for testing and not testing," basically applying here - that testing … from normally sterile sites; it may be warranted especially in immuno deficient patients saying, "You're not going to be testing these organisms routinely on isolates from all sources."

There's another little section that describes where the breakpoints or interpretative criteria, how they were derived and here it's saying, "The criteria for Penn and Erythor are based on MIC distributions following testing in a large number of isolates. …Interpretive criteria are adapted or listed from those from Streptococcus in M100 and so forth." But again too, there is a description of how those breakpoints were derived for inclusion in M45.

Then finally, some testing notes and here for Coriny, we're saying resistance results can be reported 24-hours. Isolates demonstrating

susceptible results for beta-lactams should be reincubated than results reported at 48 hours. So the format for the table for Coriny bacteria is identical for the format for the other 14 organisms or organism groups listed in the M45P guidelines. I think a lot of you have been struggling with testing some of these organisms for some time. Hopefully, this is the beginning of providing you with some additional guidance in that regard.

Now let's go on to slide 41 and let's now focus on the changes related specifically to gram-negative bacteria in the new M100 table. If we go to slide 42, just looking at those particular issues that have been clarified; ESBL screening breakpoints for Proteus mirabilis, the warning content for Salmonella and Shigella, and susceptibility testing of Salmonella species from feces. Let's talk about these in more detail.

If you go to slide 43, I just listed the screening breakpoints for Proteus … and indicating how they differ from the screening breakpoints for E. coli and Klebsiella. I have to apologize that even after reviewing this a zillion times, there is a typo here. The typo is the screening break point for septagoxine with distafusion. It should be less or equal to 22. So the screening breakpoints for distafusion in septagoxine should be less or equal to 22. The 17 is in correct.

If you go down to the footnote, that's where the 17 should be because 17 is the screening break point for the E. coli and Kleb. So if you please change on the bottom of that "less or equal to 17" in the top, the first column. It should be less or equal to 22, not less or equal to 17. But this is very nicely outline in the new tables in M100. So go by those and not my information on the slide here please.

Nevertheless, we're just clarifying what those screening breakpoints are for Proteus mirabilis. The only else I want to say about this at this time is that we still do not recommend it's necessary to screen all Proteus mirabilis isolates for ESBL production, but primarily focus on those isolates from sterile body site specimens. The reason for this recommendation at this time is that at this point in time, the incidence that the ESBL producing Proteus mirabilis is very, very low. I believe we've only had one or two isolates here at UCLA at this time. The ESBL producing Proteus mirabilis are quite prevalent, however, in other parts of the world.

Now let's go on to slide 44 and show you the change in the warning comment for Salmonella and Shigella and I've highlighted what that

change is. Basically, it's the addition of "And cephamycins." So for Salmonella and Shigella first and second generation cephalosporins and cephamycins may appear … in Vitro but are not effective clinically and should not be reported as susceptible.

If you go to slide 45; again, just to remind you where you can find the information in terms of which specific agents fall into that cephamycin subclass. You can get that information in the glossary that is in the back of M100-S16. So here too to remind you that that glossary can be very useful in trying to decipher some of the comments in our M100 standards as well as perhaps answer some questions physicians may have about specific drugs or specific drug classes.

Let's go on to slide 46 and this is another change in one of the comments related to testing salmonella. The changes here are the addition of the words "when" and "are tested." So here what we're saying is when … isolates of Salmonella and Shigella species are tested, only Ampicillin, Aquinolone and Trimeth-Sulfa should be tested and reported routinely. In addition, … and a third generation cephalosporin should be tested and reported for extra-intestinal isolates of Salmonella species. Again too, this is found in your Enterobacteraceae table and M100-S16.

If you go to the next slide, I'm just trying to illustrate what this really means. This would be a common report that you might release on Salmonella when isolated from a … specimen where you report results for Am, Aquinolone, and Trimeth-Sulfa and as indicated in that previous comment, if you're talking about an extra-intestinal isolate of Salmonella, we suggest adding quaronthenticol. This as if you're physician wants this drug. If quarothenticol is not on your routine panel, you might want to ask your physician if they really need that result before going to additional means to get Quarothenticol tested and also a third generation cephalosporin because those would be important if, for example, a physician were treating Salmonella bacterimia.

Here too, why we modified that comment related to when people isolates are tested is because there is substantial documentation now suggesting that if Salmonella is causing mild diarrhea that these infections are often self-limiting. So it may not be essential to do routine susceptibility testing on Salmonella from … sources. So this is something you might want to discuss with your medical staff. You may only wish to test these organisms for susceptibility if the physician specifically requests it. Here too, going back to the point where if we report susceptibility results,

physicians are likely to treat. If it's not essential to treat these mild cases of Salmonella, may be a good thing to do would be not to report susceptibility results routinely. So this something we all need to think about.

Let's go on to slide 48 and let's talk a little bit about the non-Enterobacteraceae and perhaps one of the major changes in M100-S16 is the addition of separate break point tables for Pseudomonas aeruginosa, Acinetobacter, Burkholderia and Stenotrophomonas maltophila.

Another change has been the deletion of the comment related to therapy for Pseudomonas aeruginosa and then a little more information about Colistin and Polymyxin B. We actually deleted the distafusion quality control ranges for both Colistin and Polymyxin B. I'll explain a little more about that in a moment. We've added Colistin MIC breakpoints for Acinetobacter.

Now let's go to slide 49. This is just a snapshot of the top of table one for the Enterobacteraceae, Pseudomonas aeruginosa and other non-Enterobacteraceae Staph and Enterococcus and then as most of you know, last year we added a separate list of recommendations for Acinetobacter,

… and Stenotrophomonas maltophilia suggesting specific drugs that should be considered for testing and reporting on those particular non-Enterobacteraceae.

This year, we went one step further, as you will see on slide 50 where we've added breakpoints for each of these other non-Enterobacteraceae groups. So now we have a separate table for the breakpoints for Acinetobacter and for Stenotrophomonas maltophilia as shown as the example in this slide right here, and also for Burkholderia Cepacia.

If you go to slide 51, let's look at the application of these new tables to Stenotrophomonas maltophilia and here, we're looking an isolate from blood, the drugs that would be considered appropriate for testing against Stenotrophomonas maltophilia and for which we have MIC breakpoints in the new table in M100. We only have interpretative criteria for these five drugs as listed on the slide right here, which are the primary drugs that would be considered for treating infections cause by Stenotrophomonas.

Now if you go to slide 52, I've posed a question here: "What if your physician asks for results for other drugs on Stenotrophomonas maltophilia?" This is a difficult organism to treat, as you know, and

sometimes the primary agents that are mostly indicated in literature may not be appropriate. Physicians may be looking for other alternative. What are the options to consider since we only have MIC breakpoints for those five drugs as shown on the previous slide?

Well to get that request in writing, preferably from an infectious disease clinician that has determined that an additional drug should be considered. Test that by MIC only. Report results without interpretation and quality the results.

In slide 53, I've showed you an optimal way to report this and here, for example, if the physician asks you about … for which we do not have breakpoints, you can report that MIC. You might want to include a comment: "No MIC interpretative criteria available. Reported per the physician's request." As some of you know, we try to put the physician's name in this particular comment. Then we add a supplemental comment here: "Infectious disease consult suggested." Again too because if a physician is asking you to test a drug that's not one of the primary recommendations, that would behoove that physician to make sure that there is an infection disease consult while be it sometimes the individual that's asking for that supplemental drug is the infectious disease clinician.

Nevertheless, there are not easy ways of handling this, but this is one possible option. Some of you may ask, "Why are there only breakpoints for these five drugs?" Well recently, the testing and the appropriate breakpoints for some of these non-Enterobacteraceae had been reexamined and it's only been in these five drugs, which are the primary drugs, the breakpoints have been reexamined and these were felt to be the appropriate break point.

Now let's go on to slide 54. Another change that's occurred with the non-Enterobacteraceae was elimination of that comment for the RX comment related to Pseudomonas aeruginosa where the comment previously said that Pseudomonas infections in … patients and serious infections in other patients should be treated with maximum doses of the selected anti-Pseudomonal Penicillin or Ceftazadine in combination with an aminoglycocide. The rationale for deleting this RX comment rather than modifying it; there are currently other options for treatment, but it was felt not to get into those in our CLSI tables. So the comment was eliminated.

What about Colistin and Polymyxin, as on slide 55. We know this is a headache for many of us in the laboratories that are being asked to test one

or both of these agents because there's not an easy way to do this. There currently are no distafusion recommendations. As I mentioned, we eliminated the distafusion quality control ranges for these agents. At the recent CLSI meetings - I just got back two days ago - this was again discussed and it's unlikely there are going to be distafusion standards for testing Colistin and Polymyxin.

What is now in our CLSI M100-S16 are breakpoints for both Colistin and Polymyxin for Acinetobacter. Those are listed on the slide right here. It's likely that breakpoints for other drugs, other organisms will be forthcoming. We should see breakpoints for both of these drugs for Pseudomonas aeruginosa and Enterobacteraceae hopefully in 2007.

One of the biggest dilemmas is there is no FDA cleared MIC testing for testing either of these agents. I know some commercial laboratories are doing this. Some may be doing it by Broth Microdilution Reference Method. I know some are doing it by E test and E test does have both Polymyxin and Colistin strips available and then reporting results for research use only.

I know this can't be tested by the CDC laboratory. You would have to go

to your local health department to get access to the CDC laboratory, which we know can result in some delays. Some other reference labs; I know our laboratory here at UCLA is testing both of these by the Reference Broth Microdilution Method and there may be some other labs in your area that can do this. I wish I had a better suggestion for you for how to deal with this but unfortunately at this time, there's not much that's better. We just have to do the best we can.

Let's go on to slide 56. There have been some changes with Haemophilus and Neisseria Meningitidis. For Haemophilus, as I mentioned, the aphrophilus group, Haemophilus are now included in the new M45P guidelines. So now, the information or the … in M2, M7 and M100 are only for Haemophilus influenza and parent influenza. Any other Haemophilus should be tested according to the recommendations found under the … group organisms in the M45P document.

From a Meningococcus, we now added a distafusion procedure. On slide 57, you will see a snapshot from that new table and here too, seeing the testing conditions … MIC, minimal quality control recommendations, the breakpoints and so forth. Now on slide 58, the distafusion testing recommendations are used … with 5% sheep blood, using the direct

colony suspension technique for innocular preparation. Incubate CO2 for 20 to 24 hours. Very specific quality control organisms recommended as well.

The one thing I have to reiterate again related to testing Meningococcus is that we all have to be exceedingly careful in working with this organism. We've all heard about the serious laboratory acquired infections when working with Meningococcus. So it is advised that this testing be performed in a biological safety cabinet.

Let's look at slide 59 and this represents the group of drugs that are listed in the Meningococcal table that would be considered appropriate for guiding therapy of a Meningococcal infection. It includes ten amp Cefataxime…. I might mention that all of these drugs are listed in ... Group C, which basically indicates these should be considered for supplement testing reporting selectively. So the implication here is that we're not advocating all clinical laboratories test Meningococcus routinely, but only if the physician were to deem that was necessary.

The other thing in terms of distafusion testing of … the penicillin and ampicillin tests don't work. So in order to test these two drugs, you would

have to use an MIC methodology.

If you go to slide 60, there are some drugs listed in the Meningococcal table where there are breakpoints for drugs that would be appropriate for prophylaxis of Meningococcal case context. So basically, the drugs listed here and the results of them would be used to guide prophylaxis of the individual that comes in contact with the patient with Meningococcal disease. These include … Cipro, Mino. Naladixic acid breakpoints are also included in that table to help to test diminished fluoroquinolone susceptibility - this is spelled out in the document - and…. It's also indicated there as this predicts susceptibility to Sulfonamides, which would likely be the agent that might be considered for prophylaxis. Again, all of these in that test report Group C. We're not saying to test these routinely but on physician request when esteemed that that would be necessary. As you know, Meningococcal infections are often created empirically and it's really not essential in all cases to have susceptibility test results to guide therapy.

Now let's move on to slide 61 and then onto slide 62. We're going to talk about some of the changes related to testing the gram-positive bacteria. Now the first slide here relates to Daptomycin and again, as a reminder,

for the Staphylococcus, Enterococcus and Streptococcus where we previously had distafusion breakpoints, these now have been deleted. The rationale for this is because it was found, after the drug was out there for a while and some non-susceptible … were encountered, the distafusion test could not consistently detect those isolates that were non-susceptible to Daptomycin. So at this point in time, we're recommending laboratories do not use the distafusion method for testing Daptomycin.

There's been a specification of the … testing has not been validated for Daptomycin. I doubt many of you are doing … testing in your laboratory, but nevertheless, this has been pointed out in the new documents. Also, I might mention that Daptomycin is now on several commercial systems and is FDA cleared and to check with your manufacturer if you're being asked to test this drug and see if you can test it by your routine systems.

If you go on to slide 63, some of the clarifications related to the gram-positives relate to Staphylococcus where we've clarified for distafusion testing the Cefoxitin. This is preferred over the Oxacillin disks for detection of … resistance. Also, the Cefoxitin disk is a surrogate for Oxacillin. We never report Cefoxitin against Staphylococcus. We only use it as a surrogate to report Oxacillin. It should always be used for….

We're saying, do not use an Oxacillin disk and other clarifications had been for the breakpoints for the fluoroquinolones and Staphylococcus and that they're going to be tentative for another year.

Now if you go to slide 64, this is nothing new. I just wanted to reiterate what those Cefoxitin disk breakpoints are for the Staphylococci. The Cefoxitin breakpoints that are there to detect … mediated resistance in the Staph. Here for Staph aureus and lugdunenis, if you were to get a Cefoxitin zone of 19 millimeters or less, you would report that organism as resistant to Oxacillin. Again, don't report Cefoxitin. There are unique breakpoints for coag negative Staph.

Now let's go on to slide 65. This reflects the current MIC breakpoints for Staphylococcus and the quinalones. There are some corresponding differences between the older CLSI documents and the documents from 2005 and now 2006 as well. Here too, you can see some differences. What I want to point out here is that although there are these changed breakpoints over the last two years in the CLSI document, the breakpoints in the current FDA product labeling are the same as those that were in the previous CLSI document.

So here too, if you're using a commercial system, the breakpoints for that commercial system will still be the older CLSI or the FDA breakpoints. If you were using a commercial system, you would have to decide if you're going to continue to use that for Staphylococcus in the fluoroquinolones or if you were going to try to validate your system with the CLSI breakpoints or use an alternative system.

I know some laboratories are continuing to use the FDA breakpoints as indicated with their commercial system. I might add that there will be very few differences for the results, depending on which set of breakpoints you use. These are still considered tentative for a year - the new CLSI breakpoints. The reason for this is to allow more time for the manufacturers to deal with the changes or deal with these two sets of breakpoints and the best resolution for them.

So I would suggest if you are reporting the quinolones against Staphylococcus you talk with the manufacturer of your commercial system and decide the best strategy for dealing with that and probably the best strategy might be to just go with the breakpoints that are indicated with that commercial product.

Now let's go on to slide 67 and talk a little bit more about the new breakpoints for Staphylococcus and Vancomycin for MICs. Here you can see, again, on the left, I have the new CLSI 2006 breakpoints; on the right were the former breakpoints that were published in 2005. Again, two or less is susceptible, four to eight is intermediate, 16 or greater is resistant.

I might mention that the 2005 breakpoints are the same as those currently published by the FDA and here a reminder that if you're using a commercial system that basically you have to follow the breakpoints for that commercial system, which are the FDA or older breakpoints, unless you are validating the newer breakpoints, which would be difficult to do. I might mention there has been no change in the distafusion breakpoints for Vancomycin for Staph aureus or coag negative Staph and there's no change whatsoever for Vancomycin breakpoints for coagulated negative Staph. So the only Vancomycin breakpoints that have changed are the MIC breakpoints for Staph aureus.

Well let's go on to slide 68: Why did CLSI modify the Vancomycin breakpoints for Staph aureus? Basically, to detect emerging Vancomycin resistance. It's been shown that patient can fail Vancomycin therapy when infected with Staph aureus with Vanco MICs at four or great. So this was

suggesting that a susceptible breakpoint of four or less was inappropriate. Clinical labs have been advised for the past few years by CDC to check any Staph aureus with a Vanco MIC of four or great as a potential VISA and if the MIC was high enough, this might even be VRSA. We know that some VISA do test four by some of the systems that are out there.

So if we go to slide 69, just to remind you, as I said earlier, that CLSI does have a mechanism to reevaluate breakpoints when it's needed to detect emerging resistance. This is described in the CLSI M23 document: "Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters."

Well let's go on to slide 70. Does matter what Vancomycin breakpoints we use for Staph aureus - if we use the older ones that are the same as the FDA breakpoints or the newer ones published in the M100-S16? Well as I mentioned earlier, that box in the beginning of M100-S16 does state that either FDA or CLSI susceptibility interpretive breakpoints are acceptable to clinical laboratory accrediting bodies. I've indicated exactly where that comment can be found.

We should all pursue Staph aureus with Vancomycin MICs of four or

greater as we did advise by the CDC. This needs to be VISA or VRSA. The actual recommendations for that are found on the Web site for the URL listed here that we talked about extensively in last year's teleconference. So basically, if we all diligently pursue Vancomycin MICs of four or greater, it really won't matter.

If we go to slide 71, I've just indicated how frequently there might be this discrepancy. This refers to about 14,000 isolates of Staph aureus that we tested here at UCLA against Vancomycin using the Reference Broth Microdilution Method. You can see that the differences between using the CLSI susceptible breakpoint or FDA's susceptible breakpoint isn't going to really matter that much if we pursue an MIC of four and also to show we only had 0.6% of these isolates with Vanco MICs of two and we only had one isolate that had an MIC greater than two and that was our one ... Strain that gave us an MIC result - I believe sometimes it was four and sometimes it was eight. But nevertheless, following CDC recommendations, we would not report that as susceptible without pursuing it extensively and working with our health departments and so forth. So here too, we need to be concerned about doing something about those MICs with four.

Let's go on to slide 72. A new addition to M100-S16 has been the addition of consolidated instructions for the BHI Vanco screen for detecting VISA or VRSA. As indicated in the CDC algorithm, again the link for finding that information is reiterated on this slide right here. Basically we're saying to add a BHI screen, if you're using an automated system, unless that system has been fixed an now can reliably detect VISA and VRSA or use the CLSI MIC reference method or E test to detect reduced susceptibility to Vanco in Staph aureus.

Now why I say, "unless fixed;" some of the commercial manufacturers have now resubmitted a modified product to the FDA, have gotten clearance. So they have now proven that their modified tests can reliably detect VISA or VRSA. Now I know I think this recently occurred with the Microscan products and I think other manufacturers are about to make these changes in the very near future. Each laboratory has to decide that if you are to continue with the BHI Vanco screenplay, but it is now legitimate to use the FDA cleared modified product without the BHI Vanco screenplay. I know some laboratories are doing this. But check with your manufacturer of your commercial product to see where they're at with this particular issue and hopefully all of us will be able to eliminate the BHI Vanco screen plays in the near future if indeed we can identify

our primary system as being satisfactory for detecting VISAs and VRSAs.

If you go to slide 73, I just listed the VRSAs that now have been reported and after yesterday's teleconference I was told that there has been a sixth VRSA and this too was encountered in Michigan. So four out of the six … that have been reported have been encountered in Michigan. CDC and Michigan Public Health Authorities are scrutinizing all the data available on these isolates to try to find out particularly what it is about Michigan where they're finding these isolates.

Now let's go on to slide 74 and talk a little bit about the very minor changes that have occurred with Enterococcus. There was been a deletion of the Vancomycin synergy therapy comment. There have been expanded definitions for high-level aminoglycocide resistance for the distafusion method for detecting this. These definitions are basically identical to those that have been previously listed in the MIC test for high-level aminoglycocide resistance.

In slide 75 you will see the comment that has been deleted. If Vanco is used for serious Enterococcal infections, such as Endocarditis, combined therapy with an aminoglycocide is usually indicated. The rational is that

the use of Vancomycin should not be encouraged. Am or Pen are the preferred agents are used as combination therapy for Enterococci. Now, we know if it's a penicillin allergic patient or if it's a … that's Am or Pen resistant, Vancomycin would be the preferred cell wall active agent. But it was felt the CLSI did not want to promote or encourage the use of Vancomycin and that this comment was eliminated.

If you go to slide 76, this is just the chart out of the M2 section of the table that describes the test for high-level aminoglycocide resistance in Enterococci … use a very special high content disk and a definition of what it means when you get a resistant, inconclusive or susceptible result would be when using this particular methodology.

If you go to slide 77, here are those definitions. We're saying if you get a resistant result, that indicates that the drug, that particular aminoglycocide will not be synergistic with the cell wall active agents. If you get an inconclusive result, the recommendation is to do an auger dilution or a broth microdilution test to confirm that inconclusive result. If you get a susceptible result, it indicates that aminoglycocide will be synergistic with the cell wall active agent. So again too, these are basically the same definitions that have been existent for some time with the MIC methods

for high-level aminoglycocide resistance in Enterococci.

Let's go on to slide 78, a very minor modification for Pneomococcus and that relates to the comment that discusses which drug should be routinely reported. Pneumococci causing meningitis. Here, we're now saying that … and Cefataxime or Ceftriaxone or Mirapenab should be tested by MIC method and routinely reported for CSF isolates. Previously, the comment was listed such that it suggested that Cafaxtaxime or Ceftriaxone and Mirapenab should be reported. But now we're saying to work with your medical staff and decide which of these would be appropriate in reporting on CSF isolates in your facility. It's not necessary to report all of these.

Let's go on to slide 14 and there are two new drugs listed in the M100-S16 - … which is a … that's administered by the IV route; Faropenem, which is a penem that has oral administration. Neither of these are yet FDA approved. They are only presented in a glossary and 2C tables in M100.

If you go to the next slide, which is slide 80, here's a little bit more about Septabipro. It's manufactured by J&J. It's possible clinical use - Nosocomial Pneumonia, complicated skin and skin structure infections. If you go to the next slide, it's just a listing of the microbiological activity of

this particular compound. It does have activity against Staph, including MRSA, Streptococci including ten resistant pneumococcus, Enterococcus vitalis, most Enterobacteraceae, HFlu including the beta-lactamase negative … resistant strains, many … and…. It has limited activity of other non-Enterobacteraceae such as Stenotrophomonas, limited activity against ephesium, ESBL producers, … beta-lactamase producers and beta-lactamase producing anaerobes.

If you go to slide 82, the other new drug, the penem, Faropenem, is manufactured by Replidyne. Possible clinical use - respiratory infections such as sinituis, … exacerbations of chronic bronchitis, community acquired pneumonia, uncomplicated skin and skin structure infections. If you go to slide 83, you'll see the organisms for which this agent has activity, the respiratory pathogens, … methasone susceptible Staph aureus, some Enterobacteraceae, limited activity against non-Enterobacteraceae, Enterobacteraceae species, Enterococcus faecium and MRSA.

Now let's move on to 84 and talk a little bit about the changes for quality control. The primary additions, the only quality control ranges that have been added for Septabipro and Faropenem. There have been some additional quality control ranges for the Helicobacter quality control

strain.

If you go to slide 86, I've just listed all of the QC tables that are now in the M2 and M7 sections of the M100. Now there are a lot of these tables threes and all of the table threes relate to quality controls. I've highlighted those which are new. The primary ones which clinical labs will be concerned about are the new institution and MIC troubleshooting guides. The new table for MIC testing of fastidious organisms are for auger dilution testing primarily of the gonococci, Helicobacter. The new table 3(d) for MIC testing in … is primarily for the agents of bioterrorism.

Then on slide 87, you will see the continuation of this summary with the MIC troubleshooting guide that is also new. Now let's go on to slide 88 and this is a snapshot of the distafusion troubleshooting guide and that for MIC testing is very similar. It reads that this table provides guidance for troubleshooting and corrective action for out of range quality control primarily using susceptibility test of … auger. It talks about referring to the distafusion document that describes more about quality control procedures. It also has a flow chart in the M2 document.

It also says, "Out of range quality control tests should first be repeated. If

the issue is unresolved, this troubleshooting guide provides additional suggestions for troubleshooting out of range of results. In addition, if unresolved, manufacturers should be notified of potential problems."

So here you can see an actual snapshot of the table itself. On slide 89, I've extracted the information for two drug groups and for example, with the beta-lactams, with any QC strains if you observe … initially acceptable but decreases and possibly out of range over time, the probable cause: The disk has lost potency. The comments or action: Use an alternative wad of disks. Check storage conditions and package integrity. Those drugs that are most vulnerable and any Penem, … and clavulanic acid.

For quinalones with any QC strain, if your zones are too large; this might be due to the PH of the media being too high and indicating what that acceptable range is. So again too, you could use this troubleshooting guide to help you troubleshoot problems and also add a reference when you're documenting what action was taken for quality control procedures. I'd encourage all of you to put a copy of this troubleshooting guide in your procedure manual.

Now let's go on to slide 90 and we talked an awful lot about M100-S16

and what about the changes in the new M2 and M7 text document that describes how to do the test? Now if you go to slide 91, the primary changes basically expand the discussions and detailed recommendations for test procedures that have been occurring in M100-S16 over the past two years. There's an extensive and lengthy description of what to do about testing for Oxacillin resistant Staph, more information on testing Pneumococcus and Streptococcus particularly in the distafusion document and also the new recommendations … great detail for testing the Meningococcus.

On slide 92, additional information, descriptions of the new antimicrobial agents, more tips for media and reagent preparation and there are some supplement quality control suggestions.

If you go to slide 93, I just want to draw your attention to that question and answer section at the back of M2 and M9 because I think there's some valuable information here for which you might learn some additional reasons as to why you're seeing some of the things you do. It's just a recap of one of these on slide 94.

So for example, and I've paraphrased this just to shorten it a bit so it can

fit on the slide. One of the questions that was submitted to CLSI that was answered by the sub committee: "What is the … test not recommended for Pneumococcus?" The answer, isolates of Pneumoccocus can have … resistance to Erythromycin. However, the vast majority of these are also resistant to … with … type of clindomycin resistance. Rare isolates of Pneumococci may have inducible resistance. However, the clinical significance of this has not been established. Therefore, routine testing for inducible clinda resistance is not recommended for the Pneumococcus.

Let's go on to slide 95 and I just recap some of the issues under discussion by CLSI. We know you all need some help for testing … and hopefully, we can come up with a more complete recommendation in 2007; a distafusion test for … for … and Cipro, more on detection of DSDO, other gram-negative beta-lactomases, reviewing recommendations for drugs in the test and report table one and reexamination of those … that suggest you can extrapolate results from one drug to another and improve communication at the CLSI AST subcommittee decision.

This is now a working group, an improved communication working group within the subcommittee. We're asking all of you that have any suggestions of how you feel CLSI can help you with newer documents,

with a better understanding of existing documents to please send in your comments to CLSI or you can send in your comments on your evaluation form from this particular program. Please let your imagination run wild here. We're here to serve you and to make as life as easy for you as possible as related to susceptibility testing.

Slide 96 just recaps the information that we provided you for this teleconference, including a PowerPoint presentation, which can be downloadable. I would encourage any of you that are doing teaching to please feel free to use these PowerPoint slides to share with others in your facility or in your microbiology community. This is not a copyrighted presentation. Our main concern here is that as many as possible get exposed to this new information.

Also the checklist that I talked about, some references and then information from CLSI as to how you can procure the documents and to get more information on this organization.

If you go to slide 97, as you can see, we've run out of time. Also because we have so many sites subscribed to this program, it would be very technically difficult to take questions live for this presentation. But we are

asking if you have any questions over the next week, please submit them to the e-mail address on slide 97. We are going to compile all of these questions and answers. When that becomes available, we will notify you and then we will post it on our Web site as we did last year.

Finally on slide 98, I would like acknowledge all the individuals that have helped me with this presentation, to include the tremendous efforts of the Boston NLTN office: Shula Escot, Denise Koreniowski, Vince Senta-Maha, Melissa…. Also, some of my colleagues at AST and CLSI have given me some suggestions, including Mary-Jane Ferraro, Jim Jorgenson, Susan Morrow, John Powers, Janice Swenson and Fred Tenover. Also I'd like to thank that I don't have on this slide, Karen Bush, Amortha McNeil and Ian Pritchly from Riplidyne who helped me with the information on the Septabipro and Faropenem.

Finally, a tremendous thanks for the financial support from Ortho-McNeil Pharmaceuticals that allows us to put this program on free of charge. We could not have done this without them and we are certainly grateful for their support.

On slide 99, just to remind you that there are a lot of other programs that

NLTN provides. This is the link to that Web site. This is where we will post additional information as it becomes available not only for susceptibility testing, but for other aspects of clinical laboratory and public health laboratory medicine as well.

Finally on slide 100, I would like to thank you so very much for listening to this teleconference. Again, I would encourage you to send in your questions, comments, suggestions, anything you could have so we could help you do the best you can in susceptibility testing your laboratories so you can encourage and help with prudent prescribing practices of our clinicians.

With that, I'd like to end and I know some of you may have logged off, but Denise probably has some final comments for us.

D. Koreniowski Yes. Thank you, Janice. It was very informative. Once again, if you have any questions, e-mail your questions to neoffice@nltn.org. Miss. Hinder will respond by e-mail. To repeat, that e-mail address is neoffice@nltn.org.

Again, I would like to remind all the participants listening in to our

program to register and complete an evaluation form by February 26th. When you have completed the registration and evaluation form, you will be able to print your continuing education certificate. The directions for this are on your confirmation letter and general hand out. Documenting your participation helps us to bring high-quality cost-effective training programs in a variety of formats.

That concludes our program. The National Laboratory Training Network would like to thank Janet Hindler and also Ortho-McNeil Pharmaceuticals for generously providing financial support for this program. I hope that all of you will consider joining us for future programs and that you will make the National Laboratory Training Network your choice for laboratory training.

From the State Lab Institute in Boston, Massachusetts, this is Denise Koreniowski. Good day.

Coordinator This concludes today's conference call. Thank you.