

at

ATDEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**MICROBIOLOGY DEVICES PANEL MEETING**  
**MEDICAL ADVISORY COMMITTEE MEETING**  
**OPEN SESSION**

Friday, February 13, 1998

10:20 a.m.

at

Room 020B  
9200 Corporate Boulevard  
Rockville, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

at

PARTICIPANTS

Lauri D. Thrupp, M.D., Chairperson  
Freddie M. Poole, M.T., Executive Secretary

VOTING MEMBERS

Patricia Charache, M.D.  
Margaret A. Kadree, M.D.  
Steven C. Specter, Ph.D.  
Carmelita U. Tuazon, M.D.

CONSUMER REPRESENTATIVE

Luis A. Rodriguez, M.S.

INDUSTRY REPRESENTATIVE

David G. Gates, Ph.D.

CONSULTANTS

Paul H. Edelstein, M.D (Temporary Voting member)  
Valerie L. Ng, Ph.D., M.D.  
Melvin P. Weinstein, M.D.  
Ronald Zabransky, Ph.D. (Temporary Voting Member)

FDA

Steven I. Gutman, M.D., M.B.A.  
Joseph Hackett, Ph.D.

at

C O N T E N T S

	<u>PAGE</u>
Call to Order	4
Manufacturer's Presentation	7
Petition Overview:	7
Ross Mulder, bioMerieux Vitek	
Regulatory Overview:	10
Thomas Tsakeris, Consultant	
Product Development:	22
JoAnna Gerst, bioMerieux Vitek	
Detection of Resistance:	36
Christine C. Sanders, Ph.D., Consultant	
Clinical Significance:	49
W. Eugene Sanders, M.D., Consultant	
Summary of Discussions and Petition:	56
Ross Mulder, bioMerieux Vitek	
FDA Presentation	62
Introduction: Steven Gutman, M.D., M.B.A.	
Summary of FDA Concerns:	70
M. Elizabeth Rogers, B.S. MT(ASCP)	
Open Public Hearing:	78
Sharon K. Cullen, Dade Behring MicroScan, Inc.	
Open Committee Discussion	85
Industry Response	121
Panel Vote and Recommendations	136
Presentation by Division Director to Luis Rodriguez	165
Adjournment	167

at

P R O C E E D I N G S

DR. THRUPP: We would like the panel and the audience to come to order. The first order of business, could we have the panel members identify themselves and give their affiliation.

DR. TUAZON: I am Carmelita Tuazon from George Washington University Medical Center.

DR. EDELSTEIN: Paul Edelstein, University of Pennsylvania.

DR. NG: Valerie Ng, University of California, San Francisco.

DR. WEINSTEIN: Mel Weinstein, Robert Wood Johnson Medical School.

DR. ZABRANSKY: Ron Zabransky, Veterans Healthcare System of Ohio based in Cleveland.

MR. RODRIQUEZ: Luis Rodriguez, San Antonio College. I am the consumer representative.

DR. GATES: David Gates, Becton Dickenson. I am the industrial rep.

DR. HACKETT: I am Joe Hackett, Associate Division Director of the Division sitting in for Dr. Gutman who will be here later this morning.

DR. KADREE: Margaret Kadree, Morehouse School of Medicine.

at

DR. SPECTER: Steven Specter, University of South Florida, Tampa, Florida.

DR. CHARACHE: Patricia Charache, Johns Hopkins University School of Medicine.

DR. TUAZON: Lauri Thrupp, University of California, Irvine.

DR. POOLE: Thank you. Today, we make the following announcement to address conflict of interest issues associated with this meeting and to make it part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda on all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employees financial interest.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Paul Edelstein, Lauri Thrupp and Melvin Weinstein. The

at

matters reported by these individuals are not related to the specific issues before the panel. Therefore, the agency has determined that they may participate fully in the committee's deliberations.

In the even that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask that, in the interest of fairness, all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Today's agenda item is a reclassification petition of fully automated short-term incubation antimicrobial susceptibility devices from class III to class II.

DR. THRUPP: To lead off the discussion, we would ask Ross Mulder who is on the agenda as the first speaker. We might, by way of format, since there are several sequential speakers, institute a national ASM meeting format where we will allow for a couple of minutes of discussion after each presentation rather than try to hold the questions all to the end.

at

There will be an opportunity, obviously, for more questions at the end, but it is sometimes fresher if we can do them right after the presentation.

### **Manufacturer's Presentation**

#### **bioMerieux Vitek**

#### **Regulatory Overview**

MR. MULDER: Good morning. I'm Ross Mulder, Director of Regulatory Affairs at bioMerieux Vitek. I would like to thank the FDA and the panel on behalf of bioMerieux Vitek as well as all the other manufacturers affected by this petition for allowing us to present to you today.

Following my comments, Tom Tsakeris, President of Diagnostics Consulting Group, will give you a regulatory background and overview and the status of the short-term incubation cycle antimicrobial susceptibility devices. Then JoAnna Gerst, who is Manager of Biosciences at bioMerieux Vitek, will present a short discussion on development of Vitek susceptibility tests from which you will be able to see the relationship with the FDA regulations.

Then Dr. Christine Sanders from Creighton University and Director for Research and Anti-infectives and Biotechnology will present information on resistance and detection of resistance. Then Dr. Eugene Sanders, with the

at

same affiliation, will discuss the clinical implications of having susceptibility results in a timely manner.

The premise of this petition is that current classification of short-term incubation cycle systems as a class III PMA device is no longer necessary based on the history, technical knowledge, guidance documents and standards that are currently available and used by the FDA for the evaluation of these devices.

We are seeking, in this petition, to reclassify short-term incubation cycle systems from class III to class II. A key criterion for placing a device in class II is the availability of special controls such as accepted FDA guidelines or consensus standards that can be applied to insure the safety and effectiveness of the device.

Our petition identifies two documents which can be identified as special controls, FDA's currently used review criteria for antimicrobial susceptibility devices and the NCCLS performance standards for susceptibility testing.

The reclassification of short-term incubation cycle systems to class II will not change any of the performance requirements which are currently in effect nor FDA's ability to require safety and effectiveness data on the products. Therefore, reclassifying these devices will not change the assurance of safety and efficacy for them.

at

The focus of the current FDA process is detection of resistance. Until that can be shown, a device will not receive approval or clearance whether it is short-term incubation cycle or an overnight system. A limitation statement must be included in the labeling with either type of device if there is insufficient performance data to demonstrate that it can detect resistance with specific antibiotic organism combinations.

The other controls associated with a class II device would include device registration, medical device reporting, good manufacturing practices which is set forth in the new quality systems regulation.

In particular, the new quality system regulation strengthens the required controls for design, manufacture, packaging, labeling, storage, installation and servicing of all devices. With the regulation, there is less need for the extensive design and manufacturing information of a PMA submittal in order for FDA to insure appropriate controls in these areas.

Reclassification into class II will allow for more expeditious review process. This has become critical in today's environment where organisms are becoming more resistant at an alarming rate. Standard methods are being modified and interpretation ranges being changed in order to

at

detect strains for developing resistance.

To address this public-health issue, both FDA and diagnostic manufacturers must have a process which allows rapid review of modifications necessary to maintain the performance of their systems.

Although the FDA has made significant progress in the last year in shortening review times, with budget cuts, Congressional actions, FDA and divisional priorities, we may not always be able to count on this being the case.

Moving short-term incubation cycle antimicrobial susceptibility devices from class III to class II would provide for a more efficient review process which would enable manufacturers and FDA to keep hospital laboratories current with methodologies for detection of emerging resistance.

Additionally, this reclassification would not increase the potential for unreasonable risk to patients with the use of these devices. Last year, bioMerieux Vitek sold over 12 million test kits which relates to 120 million MIC results. We did not receive one report that the use of a susceptibility test caused a death or injury.

In fact, we have not received one report to that effect over the last 20 years nor are we aware of any other manufacturer of short-term incubation cycle devices

at

receiving any such reports.

Having given you the basis of the petition, I would now like to introduce Mr. Tom Tsakeris, President of the Device and Diagnostic Consulting Group to give you an overview of these devices.

If anybody has any questions, I can answer those quickly.

### **Regulatory Overview**

MR. TSAKERIS: Good morning Mr. Chairman, Madame Executive Secretary and members of the FDA panel. I am Tom Tsakeris, regulatory consultant to bioMerieux Vitek, the sponsor of this reclassification petition.

I served with FDA for over 23 years, 18 years in the area of clinical laboratory devices regulation. During my service with the Division of Clinical Laboratory Devices which concluded in 1993, I served as the executive secretary of this panel from 1975 to 1984 and am intimately familiar with the regulation of antimicrobial susceptibility devices.

I have been asked to speak to you today to provide an historical perspective on the regulation of these devices as well as provide some of my own insights on FDA's evolving premarket evaluation programs which apply to all clinical laboratory devices and also how some of these recent changes could effectively affect the future regulation of

at

antimicrobial susceptibility tests, which I regret that I will refer to as STIC-type ASDs, short for "short-term incubation cycle antimicrobial susceptibility devices."

First, the historical perspective. As you are now well aware, based on information contained in the petition, STIC-type ASDs, unlike all other types of other antimicrobial susceptibility devices, are classified into class III and, therefore, have been subject to the highest level of premarket scrutiny for over 20 years.

When FDA was first given authority to regulate medical devices under the Medical Device Amendments of 1976, all antimicrobial susceptibility products were considered, at that time, transitional devices and, therefore, automatically classified into class III.

The refresh your memory, transitional devices are those devices which, prior to the enactment of the date of May 28, 1976, have been previously regulated as either drugs or biologics. Up to that time, the overwhelming majority of ASDs were in the form of agar-diffusion disks and antibiotic powders.

In addition, some of you may remember the Autobac<sup>®</sup> EI, sponsored by Pfizer Diagnostics, which represented the first attempt to automate susceptibility testing. In 1982, upon the recommendation of this panel,

at

FDA formally classified by regulation all agar-diffusion disks and antibiotic powders into class II but retained the class III status of all other types of ASDs.

Some of the newer ASDs appearing during this time are commercial manual microdilution plate versions of the commonly accepted broth-dilution methodology in addition to automated and semi-automated versions requiring either standard overnight incubation of STIC-type instruments.

In 1983, FDA received a reclassification petition seeking reclassification of both manual and standard incubation-based semi-automated ASDs into class II. The petition did not address fully-automated STIC-type devices or antimicrobial susceptibility devices intended for susceptibility testing of anaerobic bacterial pathogens.

The Microbiology Panel considered the petition and recommended reclassification. Subsequently, in a 1984 Federal Register notice, the FDA significantly noted that the panel's recommendation was based on "the current availability of nationally recognized voluntary standard reference methods."

As the panel considers the merits of this present petition, I urge that it keep in mind that the reclassification process encompasses the very same fundamental criteria that applied to classification, itself.

at

In particular, an important goal of the classification process is to seek the least restrictive level of regulatory control necessary to insure the safety and effectiveness of the device.

The least restrictive control concept is a fundamental tenet of the regulatory process first envisioned by Congress in 1976 and reaffirmed by the Congress by way of the Medical Device Amendments of 1990 and, more recently, the FDA Modernization Act of 1997.

Throughout the evolution of medical device legislative initiatives, Congress has envisioned a dynamic, regulatory process in which devices, subject initially to a certain level of regulation, might change as their safety and effectiveness and risk benefit is better understood by FDA and the medical community.

Indeed, the reclassification provision contained in the Medical Device Amendments of 1976 is clear evidence of Congress' intent that the FDA apply the least restrictive control concept whenever appropriate. Up to now, the reclassification petition process has been very rarely used, either by FDA, medical device sponsors or other stakeholders of the regulatory process.

This is due, in part, to the exceedingly complex and time-consuming administrative process that has

at

previously been required. Fortunately, this situation is changing. Over the last few years, FDA, recognizing the need to focus its limited resources on devices with higher risk-benefit considerations, has taken significant steps towards realigning its regulatory priorities as part of this administration's National Performance Review Program to reinvent government services.

In particular, the FDA has been carefully reviewing how it regulates various product categories, especially those devices regulated under class III controls for extended periods of time such as STIC-type ASDs to determine whether alternative ways to regulate these devices are appropriate.

Congress has assisted FDA in this regard by broadening the criteria for assigning devices to class II controls by making available to FDA the application of special controls such as guidance documents to be used by device sponsors to provide FDA with a reasonable assurance of device safety and effectiveness.

Moreover, FDA has encouraged manufacturers to assist FDA in this activity by repositioning the reclassification process as a more expedient means to effect changes in the way devices are regulated without compromising scientific scrutiny of safety and

at

effectiveness.

A recent, notable example of the success of this process occurred last year when FDA officially reclassified serum tumor markers used to monitor cancer patients. Like STIC-type ASDs, serum tumor markers have been subject to class III PMA controls for over 20 years.

I would like to now briefly discuss some of the more significant aspects of FDA's premarket evaluation program that I believe can have a significant impact on insuring continued safety and effectiveness of these types of devices.

First, it is important to recognize that the overwhelming majority of proposed new clinical laboratory devices, about 500 to 1000 a year, reach the market through the 510(k) process. For example, the FDA has cleared, through this process, tests for new bone marker assays, new cardiac marker assays and a multitude, as you know, of nucleic-acid hybridization assays used in a variety of diagnostic applications.

It is clear that FDA has historically exercised considerable discretion and selectivity when deciding which new test should be subject to class III premarket approval evaluations. This is because once a product is subject to class III PMA controls, all other products like it are also

at

subject to the same level of review, thus requiring a major expenditure of resources both for the affected manufacturer and FDA alike.

Another major implication of placing tests into class III premarket approval is that FDA is often faced with the prospect of having to perform iterative evaluations of similar tests long after the initial unique safety and effectiveness issue that triggered their class III PMA status in the first place.

For example, when FDA determined that a new test requires a PMA application as a result of a particular question or questions about its safety and effectiveness, once these questions are satisfactorily addressed in an initial PMA review, all other similar devices which follow should no longer have the same questions given a demonstration of similar analytical performance characteristics.

In effect, this type of an evaluation becomes reduced to one of substantial equivalence rather than an evaluation of a unique safety and effectiveness question. Over the last few years, FDA has instituted a number of steps to streamline the premarket review process.

In 1993, FDA initiated a premarket application triage program that was intended to allocate more review

at

resources to higher-risk devices while deploying fewer resources to less risky ones. Also, the Safe Medical Devices Act of 1990 explicitly affirmed FDA's prerogative to obtain clinical data to support 510(k) reviews.

In fact, FDA's Division of Clinical Laboratory Devices has disseminated a draft guidance document to manufacturers entitled points to consider for the collection of data in support of in vitro device submissions for 510(k) clearance.

This document, in conjunction with other reprogramming premarket review initiatives, positions FDA to expand the scope of the 510(k) process thus allowing it to perform a more focussed review on unique lab devices which present some unique scientific issues.

Such an enhanced reviewed 510(k), the resulting product of a mix of newly formulated programs, policy and management initiatives, judiciously combines those elements of the premarket approval process with those of the 510(k).

For example, an advisory panel meeting can be convened to discuss a unique scientific or clinical issue for devices assigned to an enhanced-review 510(k). As an example, the Immunology Devices Advisory Panel was recently convened a couple of months ago to give advice to FDA on the scope of the clinical data requirements needed in 510(k)

at

submissions to evaluate the safety and effectiveness of the aforementioned reclassified serum tumor markers.

Thus, the 510(k) can be an effective regulatory instrument to assess STIC-type ASDs as a generic product group once reclassified since it contributes to more expeditious product reviews without compromising scientific scrutiny and, at the same time, avoids the prospect of making repetitive evaluations of essentially a substantial equivalence nature under class III PMA.

Moreover, FDA still retains its prerogative to assign certain ASDs to class III premarket approval should an extraordinarily new or unique safety and effectiveness concern emerge from the 510(k) review. Such might be the case; for example, for a new type of antimicrobial test methodology for which there is little or equivocal validation data to support intended-use claims.

In conclusion, STIC-type ASDs are excellent candidates for reclassification since their safety and effectiveness is much better understood today than 20 years ago when FDA first took action to actively regulate them. The reclassification of STIC-type ASDs is consistent with the least restrictive control concept that applies to the classification of all other medical devices including all other types of ASDs.

at

Reclassification of STIC-type ASDs will not sacrifice FDA's ability to conduct rigorous scientific scrutiny under the 510(k) process since clinical data requirements supporting their safety and effectiveness would not be expected to change as all relevant scientific issues could be appropriately addressed.

Therefore, I urge the panel to take this opportunity to assist both FDA and STIC ASD manufacturers toward insuring that the future regulation of these important products is commensurate with the risk and benefits of their use such as reclassification would evidence.

Thanks very much. I would be happy to answer any questions.

DR. THRUPP: Any questions for Mr. Tsakeris?

DR. EDELSTEIN: Could you summarize, very briefly, for me, please, the benefits to your company of reclassification in terms of what you would perceive as having to do differently?

MR. TSAKERIS: Actually, there are members of the company that probably can address this better than I because they are actually involved in the preparation of submissions and interfacing with the FDA. I think the major benefit here is one of a more efficient administrative process.

at

Preparing 510(k) submissions--there is a different impetus in terms of the review times. It is a much less complicated administrative process in many aspects. You asked me to summarize, so I am not going to go into detail. In my opinion, after having served a long time at the FDA, hour for hour that a reviewer spends on a 510(k) submission is more efficient time spent in that review than, perhaps, in some premarket approval applications simply because there is a lot of overhead involved, administrative overhead, in the processing of PMAs.

Having said that, I will also hasten to add that many of the changes that have occurred over the years as these STIC-type ASDs have evolved have been supplemental PMAs. They haven't been original PMAs. The FDA has made a lot of progress in turning over those reviews pretty rapidly.

But the process is still a lot different. I think the review that is applied to a 510(k), although the validation requirements and the rigor of the review would not change, the process is much simpler and it is more conducive to a more efficient review.

If you can just look at the statistics on the number of days, the FDA's own statistics on the number of days, that it takes to process PMAs, PMA supplements versus

at

510(k)s, I think those statistics, which you may want to ask the FDA to give you, will be dramatic.

DR. THRUPP: Perhaps some of these issues will be addressed by your next speaker

MR. TSAKERIS: Indeed.

DR. THRUPP: Let's move on. Dr. Zabransky?

DR. ZABRANSKY: Tom, don't run away. How will the revisions that have been recently made in the GMP inspection process be--how will the company respond to some of these revisions with a change from III to II?

MR. TSAKERIS: There really wouldn't be any. They are subject, as you know, to GMP requirements including the new quality system--

DR. ZABRANSKY: But the GMP requirements have been modified in the stence of the types of reports and the frequency of inspections and that kind of stuff. So, as far as whether it is a III or a II or a I-

MR. TSAKERIS: It doesn't make any difference. It may have a bearing and, again, this is a question that you can address to the FDA, itself--it may have a bearing on the frequency of those inspections. But, as far as the compliance with the new quality system regulations, and all of the changes, it applies equally well.

DR. THRUPP: Thank you, Tom.

at

Let's go on to JoAnna Gerst.

### **Product Development**

MS. GERST: Good morning. My name is JoAnna Gerst. I am the Manager of Biosciences at bioMerieux Vitek.

[Slide.]

I would like to spend a few minutes this morning to describe our susceptibility product development process that is employed at bioMerieux Vitek. The goal of development is to establish the conditions of reliable, rapid antimicrobial susceptibility testing.

Our product design goal is accurate, rapid MIC determinations as well as resistance detection. During our product development, we follow established control procedures as required by the quality systems regulations. These procedures are not driven by our device classification.

This should be true for other antimicrobial susceptibility test manufacturers as well. A new product development is initiated by the receipt of a specific marketing requirement. These marketing specifications detail the market needs. In the requirements document, there is an establishment of the specifications for the product such as which species would be included as well as what MIC ranges would be appropriate for the antibiotic.

at

Additionally, the requirements determine the criteria for acceptance. These are internal bioMerieux Vitek criteria but I must say that they never are less stringent than the FDA criteria and, at times, more stringent.

The development then follows a plan which the bioscientists create to address the marketing requirements.

[Slide.]

Our development process incorporates three phases. The first is predevelopment, sometimes referred to as applied research. In this phase, we establish the test parameters for the development process.

The second portion is the actual development in which we establish performance equivalent to the reference method. Finally, the third or validation stage, confirms this performance.

[Slide.]

If we take a moment to look at each of the phases in more detail, we can begin with the pre-development studies. These studies optimize the test conditions for development. The first aspect of pre-development is the selection of the media to be used in the product. The media choice begins with the NCCLS recommendations.

However, we may take the opportunity to make

at

modifications to the media to achieve optimal performance in our product. An example for this is in the testing of vancomycin with the enterococci. We found that if we employed a media that was controlled for the amino acid content, we were able to enhance our detection of the van-B genotype of enterococci.

The next aspect of pre-development includes a selection of antibiotics and the definition of the MIC range that would be employed. This is a reflection of the market needs but, obviously, the ability to detect resistance is inherent in the market requirements.

An example of the importance of this aspect is also noted in vancomycin testing, but this time with the staphylococci. It is important to be able to separate the population of staphylococci with MICs of less than or equal to 4 mcg/ml to vancomycin from those that have higher MICs. This is important to comply with the CDC's most recent recommendations on vancomycin testing.

In order to do this, the MIC test range must go beyond that MIC class.

[Slide.]

A third aspect of the pre-development studies is selection of strains. We select the strains from our collection that are appropriate for testing for the

at

particular development. We have access to strains from a global collection, so our strain is not only collected and maintained in the United States but also those from our sister laboratories in Europe and the Asia Pacific region.

We also have the ability to obtain strains from pharmaceutical companies as needed in order to supplement our collection. This is especially important for new antibiotics for which resistant strains are limited.

Our strains are characterized genotypically and/or phenotypically. For a particular development, we choose strains to represent a broad range of MICs and to address specific mechanisms of resistance. Additionally, we strive to include relevant species for a particular antibiotic development as well as strains from a variety of geographic origins.

For example, the strains that were used in our vancomycin test development, the enterococci were all genotyped for their van class.

[Slide.]

The second phase of product development is the actual development phase in which we build the database of knowledge for our product. In order to do this, we produce an experimental test kit with a large number of concentrations of antibiotic that extend beyond those that

at

will be in the final test kit.

We test this experimental card concurrently with the NCCLS reference method. On occasion, we test more than one NCCLS method as a matter of course in the development. This is true, again, during vancomycin development where we not only established an MIC value for each strain in our development collection but also performed an agar screen test.

The data then is used to build or analysis. We do this by working with the statisticians in our R&D group to establish a mathematical relationship between the growth in our test kit and the reference method MIC value. At this time, we also determine the needs for the addition of special analysis that might be necessary to optimize the detection of resistance.

For example, with vancomycin. If growth in the vancomycin well does not quite reach the threshold, we have the ability to extend incubation hour by hour so that we can provide the opportunity for resistance to be detected if it is present.

Finally, the development phase, we take the product to an external site to do a development trial. This is not to be confused with the FDA trials that happen later on during our process. The development trial has two

at

purposes. The first is to confirm the performance from the internal studies and the second is to provide is an opportunity to incorporate additional strains into our database, thus enhancing its robustness.

[Slide.]

The final phase of the product-development process is the validation phase. We have both internal and external validation. Our internal validation includes testing of the CDC challenge set and reproducibility testing. Additionally, we do robustness studies which challenge the parameters that the user may incorporate during their day-to-day testing.

These include variabilities in the isolation media, the age of the culture and the suspension age. Additional, we have ongoing shelf-life studies.

At this point, we are actually at the end of the development process. After a performance review, we turn the development over to our regulatory affairs department where an independent group manages external studies. These studies of both the protocol and the approval criteria are prescribed by the FDA.

Thank you. Any questions?

DR. THRUPP: I have one question. In your pre-development, while then proceeding to development

at

phases, have you found the NCCLS M23 document to be of assistance to your own development as well as to facilitate providing data for the FDA?

MS. GERST: We are not held to the bounds of the M23 document but we do address many of the same considerations that are in place in the M23.

DR. EDELSTEIN: You described the development phase. There have been a number of problems with both your device as well as the device made by other manufacturers that have been detected during the post-marketing phase. Examples are Klebsiella-ofloxacin discrepancies, problems with inoculum density and detection of beta-lactamase-producing organisms that were falsely called susceptible and, in fact, they were resistant, incorrect detection of resistant enterococci and pneumococci.

I would be interested to know something about that process as well.

MS. GERST: This kind of goes into the regulatory department.

MR. MULDER: There are a lot of issues that arise just because of the numbers of strains that, once a product is introduced, the number of strains that test kits are actually exposed to. So we constantly monitor the situation in the field. We have a very good relationship with our

at

customers when they do see issues with the product that they let us know and we are able to make modifications in the product.

With the changing of the organisms, that is something we have to constantly do. Unfortunately, it doesn't stand still and, during our development, after we develop, the organisms don't change. We have to keep monitoring the situations and we have to keep training our customers to set the product up according to the package inserts. We do find, a lot of times, it is in the setup process of the way they look at the product.

DR. EDELSTEIN: Maybe I can be a little more directive. When you are notified of a product failure or discrepancy--let me just give an example of inability or discordant results with Klebsiella and ofloxacin, just to use this specific example, at which point do you notify FDA?

MR. MULDER: We usually get the customer organisms in-house because there will be certain occasions that we don't detect it, there is a problem. But we always make sure that it is not hospital-specific, that it is a specific problem overall with the product. Once we determine we don't meet our performance specifications that were approved, then we have to notify the FDA.

Then we will take a limitation on that combination

at

until we can resolve the issue.

DR. EDELSTEIN: Will that requirement change or what you do change if the product is reclassified?

MR. MULDER: No. That remains exactly the same. Until we can submit performance data showing that we can remove that limitation to the FDA, that limitation will stay in place.

DR. EDELSTEIN: But in terms of the notification process, does that change at all?

MR. MULDER: No. That is regardless of class.

DR. EDELSTEIN: In terms of annual reporting which, I understand, you are currently under obligation to do?

MR. MULDER: Right.

DR. EDELSTEIN: Would the items that are in the annual report still be reported to FDA regardless?

MR. MULDER: No; we would not be required to submit an annual report if we changed classifications.

DR. EDELSTEIN: But would there be some items in the annual report or that would not come to notice of FDA if you no longer have to submit an annual report? This is something that I am trying to understand what the change in the process is.

MR. MULDER: The annual report, we submit any

at

changes that we have made in our product that we haven't notified the FDA on such as manufacturing changes on the manufacturing line, any of those things. We will have to keep all of that information in the files, any validation that we validated a new piece of equipment that was put on line, that we increased the speed or decreased the speed of something.

All that is still there for review but we don't notify the FDA of that issue--as well as articles. We send in any articles that were published during the year that we are aware of on our product.

DR. EDELSTEIN: So, to summarize, is it fair to say that any problems that affect test performance would be reported regardless of the classification.

MR. MULDER: Correct. And any notification to our customers from the company also goes in to the FDA. If we do not meet our performance claims of our product, we have to notify the FDA.

DR. EDELSTEIN: Thank you.

DR. CHARACHE: Two questions, one pertaining to validation. Since we know that the greater-than-16-hour devices are now considered class II, what I am most concerned about are those in which the results are likely to be different for the less-than-16-hour testing than they

at

would be after overnight incubation.

Those are heavily directed towards organisms whose mechanism of resistance is inducible enzymes. As you develop your validation strategy, to what extent to you specifically compare or look for species antibiotic combinations that we know to be hot trouble spots? How do they get specially challenged?

MR. MULDER: We definitely now initiate panels specifically to challenge the antibiotic. But what we will do when we initially develop is basically look at all organism groups calling at the same hour and what happens and compare those to the overnight methods.

What we will find there, most of the time, is that there are certain species and antibiotic combinations that we will call sensitive at four hours and, because of that, we are able to extend the incubation for certain antibiotic organism compounds to longer periods of time so we give the resistance a chance to express.

So we can incubate out to--we look at calling at hour 4, but then we will extend incubation to hour 8, 9, 10, up until 15. We specifically have, like, the CDC challenge set and we know what organisms we need and they are defined by the FDA that we have to have so many resistant isolets of which species to--say, cephalosporins or to penicillins.

at

They define we have to have so many resistant isolets.

DR. CHARACHE: Understanding that you can extend it, my question is how do you--according to M23, as an example, it requests that one assess organisms not only of known--that are problematic when a given species is tested against a given antibiotic, it's the pair that is the problem, but also that one, when possible, challenge strains that are known to have different mechanisms of resistance.

My question is how does your study design address such considerations. I know that the FDA requirement is only 300 strains to be tested in three laboratories. My question is how do you specifically insure that this less-than-16-hour issue is appropriately addressed?

MR. MULDER: Again, like JoAnna had said, it is by the use of collections of strains from various--we have a lot of strains from France and from Japan and from the U.S. Our basic development usually runs about 1,100 to 1,200 organisms in our internal database.

Now, if it is a cephalosporin we are looking at, we definitely look at the different types of organisms producing cephalosporinases that we know are resistant or that develop resistance to these isolates.

Then, in the development trials that are at the end of our development phase, we will specifically go to

at

various laboratories and have them challenge it with their challenge sets of organisms to make sure that we have covered all of the different mechanisms of resistance. Dr. Sanders will speak a little bit to that, but we are very aware of the organisms that we need to be aware of, and we particularly try to challenge the system with those types of organisms.

DR. THRUPP: Could I come back, for a moment, to the question that Dr. Edelstein raised in terms of a generic process that you are going through. You have described a system of interaction, once marketed in the field, to produce any indication of problems out there. He raised the example of the ofloxacin/Klebsiella. Is your process for detecting these problems one that is predesigned by systematic sampling of performance in the field by 30 or 50 or whatever labs that you have developed yourself? Or is it a process that was suggested by the FDA?

MR. MULDER: It is process we have to have in place because of the FDA. We have not specifically designed a process for that. We have to have a procedure in place to handle customer inquiries and complaints. We have to resolve those inquiries and complaints.

DR. THRUPP: But it is passive in the sense--as far as what has been required, it has been passive in the

at

sense you wait for the complaint to come? I am concerned in terms of a generic reclass move where there may Vitek may become the predicate for somebody else who does not pay attention to regular user conferences, et cetera, as you all do.

So I am wondering if there is a requirement for proactive as opposed to passive checks on problems in the field?

MR. MULDER: It can be not just customers calling you, but once you are aware of any issues with your system, they have to be investigated per FDA requirements. So if somebody publishes a paper, not necessarily notifying you, but if you read it in the literature, you have to--and it is the same for class III or class II. It is not based on your class. It is part of the requirements, the quality-system requirements, that all manufacturers have to follow.

DR. THRUPP: Dr. Zabransky?

DR. ZABRANSKY: To follow up on this. You mentioned Klebsiella/oflox. Let's look at the visas and the versas. Are you constantly seeking these organisms? Were you? Or did you respond to somebody finding this in Japan or the two or three that have been found in this country, and how fast did you get hold of these organisms or change your processes to ask laboratories to look for these

at

organisms?

MR. MULDER: How quick did we respond? We received the organisms that CDC have received in probably a month. We probably had 300 to 500 phone calls asking does Vitek detect these within that time? You know, people in the field are definitely aware of this and they want to know do their systems work with these strains.

Even though there have only been six or seven isolated in the whole world, they want to know does your system work with these. If I have one, will I find it? So we have to respond very quickly when something like this appears. CDC works well with companies making strains available to them.

The one thing that companies don't want to do is make a change based on one or two aberrant strains. So, making a change just because one person sees a resistant isolate, you have to be careful. So you can't just go make changes quickly. You have to make sure that it is a well-thought-out and a validated change.

DR. THRUPP: Any other questions? If not, thank you, Ross.

MR. MULDER: Now Dr. Christine Sanders will discuss resistance.

#### **Detection of Resistance**

at

DR. C.C. SANDERS: Thank you. It is a privilege and a pleasure to be with you this morning to discuss antimicrobial susceptibility tests, more specifically, the ability of these tests to detect resistance.

[Slide.]

Just a little historical review. As susceptibility tests moved out of the totally manual overnight arena and into the partially to fully automated and rapid arena, our focus on development of these tests went from the focus on is the test reproducible--namely, will it give us the same answer if we ask the same question 100 times--to one of accuracy--does it give us the right answer when it gives us an answer?

When we were first focussed on reproducibility, this meant that we had to focus on strains that gave us results within the range of concentrations being tested with the device; namely, sensitive strains.

So when we were focussing on reproducibility, we were focussing on sensitive strains and ignoring the off-scale strains; namely, the resistant ones. So, with some susceptibility test systems, we woke up and realized one morning that we had precisely incorrect tests. They always gave us the same answer but it was the wrong answer.

So we started to change our focus more on the

at

accurate detection of resistance.

[Slide.]

I think our focus toward the accurate detection of resistance arose from a variety of occurrences. First, resistance, indeed, is increasing in prevalence. Certainly, if you just look at the simple example of ampicillin resistance in our E. coli over last decade, it has increased nationwide from around 20 percent to now over 30 percent of all E. coli.

So, certainly, we have an increased prevalence of resistance and we are now seeing new forms of resistance that many of our susceptibility test devices do not accurately detect. Vancomycin resistance is one that has already been discussed this morning, a particular problem with many of the systems, not just the rapid systems, and the extended-spectrum beta-lactamases, or ESBLs in gram-negative organisms, a definite problem for all of our susceptibility test systems because none of the currently available systems accurately detect clinically relevant resistance in all of the strains that possess these extended-spectrum beta-lactamases.

[Slide.]

There have been a number of approaches to improve the detection of resistance in our susceptibility test

at

systems. Really, all of my comments relate to susceptibility test systems in general and are not specifically related to rapid susceptibility tests.

Certainly, one of the most important developments in improving our ability to detect resistance was the promulgation by the FDA of the review criteria for the assessment of antimicrobial susceptibility devices. In this document is the requirement that, regardless of how the susceptibility test is performed, that it must meet certain performance criteria; namely, the very major error or a false susceptibility.

The very major error rate cannot exceed 1.5 percent and the major error rate, or false resistance, cannot exceed 3 percent. In the same document is detailed the types and numbers of organisms with resistance and that different types of mechanisms of resistance must be tested before any device can get approval for use with certain bug-drug combinations.

The CDC, along these same lines, have developed a challenge panel. Certain numbers of strains of this challenge panel must be included in the isolates that are tested to develop any new device. I think this has made it a lot easier to collect resistance strains that might otherwise not be found in routine collections.

at

The manufacturers of these devices have taken great pains to collect strains with known resistance mechanisms realizing that resistance is not a static parameter but one that is constantly changing with new resistances arising.

Certainly, those of us in the scientific community have been well aware of problems with resistance and we are trying to identify new forms of resistance as they arise, identify limitations of currently existing systems in detecting new forms of resistance and working with the manufacturers to try to make changes in these devices so that new forms of resistance can be accurately dealt with.

[Slide.]

In the past, in order to see if a device could accurately detect resistance, the approach was just to test large enough numbers of strains that, just if we tested enough of them, by chance, we would catch sufficient numbers of resistant isolates to be able to show that a device could accurately detect resistance.

Unfortunately, this "by chance" approach led to only the discovery of the most prevalent types of resistance to any particular drug and, usually, these types would be clustered among very few genera of organisms. I think imipenem is an excellent example of this type of problem

at

where the most prevalent form of resistance to imipenem was seen among *Pseudomonas aeruginosa* and *Stenotrophomonas multiphilia*.

Certainly, resistance in these organisms was not predictive of the kind of resistance we are seeing today in emerge among *Enterobacter* and *Serratia*. So, to try to avoid this type of "by chance" encounter with resistance, today's major approach is to create a panel of organisms that are clinical isolates but they have been collected and designed on purpose to include a variety of all the known mechanisms of resistance to any particular drug that is being developed on any particular device.

[Slide.]

In 1991, I kind of described this type of panel. I named it the predictor panel because it is designed to predict whether or not any susceptibility test that is being developed with any particular drug to predict whether or not it could accurately separate the sensitive isolates from the resistant isolates.

We put together a predictor panel by first asking what organisms is the drug indicated for. We want to be sure, in this panel, we include all of those species and genera where the drug is likely to be used. Then we need to ask the question of what mechanisms of resistance might be

at

encountered among these organisms and make sure that when this final panel is put together, it includes both sensitive and resistant strains for the drug under study.

Ideally a 50:50 mix of sensitive and resistant strains should be included. With some drugs, that is not possible because there are not that many resistant strains out there. But this type of approach is relevant for all forms of susceptibility tests and has helped us identify the strengths and the limitations of each of those available today.

[Slide.]

We have looked with a variety of different predictor panels to various microdilution systems, all the rapid systems that are currently available today, the E-test, the good old standby disk-diffusion test. As I mentioned, we have found significant deficiencies in each of these.

For example, one deficiency that many of you in this room are aware of because you have heard me talk about on previous occasions is with the disk-diffusion test. When we subjected timentin disk to a predictor panel that included a large proportion of E. coli and Klebsiella that were resistant to the drug, the disk-diffusion incorrectly, with current criteria, identified incorrectly resistant

at

strains as sensitive with a very major error rate of 69 percent.

Those criteria for the timentin disk through the NCCLS has been changed to try to eliminate this problem. But, once again, it shows that until you use the right panel or get the right collection, sometimes you are not asking the right question and, thus, regardless of the type of test, you need to be constantly on the watch for new forms of resistance that were not available when it was originally developed and then go on to update your parameters as new forms arise.

[Slide.]

We have recently completed a collaborative study with Vitek where we were reexamining the database that is used to interpret results with gram-negative organisms and beta-lactam antibiotics. What we did in this study--as you have heard, Vitek maintains a very large collection of microorganisms that they have collected worldwide.

Many of these are well characterized as to their mechanism of resistance. Over the 25 years that I have been in business, I have collected a large number of strains worldwide also and have identified their mechanism of resistance.

From the two organism collections, we put together

at

a panel of 344 isolates that we tested. These were all gram-negatives. They include Acinetobacter, Enterobacteriaceae and Pseudomonas aeruginosa. I am just showing you the results for two drugs, ceftazidime and piperacillin.

For ceftazidime, among the 344 strains, 121, or slightly over a third of them, were resistant to ceftazidime by an NCCLS standard procedure. We then evaluated susceptibility using the Vitek test under its current database and under a new database that was developed as a result of this study.

Essential error here, listed, is the number of times the Vitek result agreed within one dilution of the standard NCCLS agar-dilution procedure. Here you have the percent very major error or the number of resistant strains that were incorrectly called sensitive by the Vitek system.

If you look at all strains in the 344, for ceftazidime, under the current database, essential agreement was 83.7 with the very major error rate being 16 percent. Under the new database that has been developed now, we have improved these problems that the essential agreement now is 99.1 percent with no very major errors.

If you look within the 344 strains, based on specific mechanisms of resistance--here is acquired

at

penicillinase. This is your high-level cephalosporinase resultant from derepression of an inducible beta-lactamase.

Here is your extended-spectrum beta-lactamase. You can see that the essential agreement and the very major error does vary depending on the mechanism of resistance. But, by putting together this predictor panel, we were able to correct these problems and bring these parameters into line with the current recommendations.

The same is true with piperacillin. Many more strains were resistant. Again, our current database gave us 77.3 percent essential agreement with an 18.7 percent very major error and this has been improved to 97.1 with a 1.4.

So I present these data to you as evidence that, indeed, even after a system is available, the manufacturers are very much aware of problems with emerging resistance. There are very important studies going on to try to accommodate to these new forms of resistance and, therefore, bring these devices into line be a rapid system or an overnight system.

Certainly, as the organisms change, we, too, must change our susceptibility test parameters to be able to detect these forms of resistance.

[Slide.]

So, in summary, I have tried to present to you

at

today the fact that the predictor panel approach, which is being used by a variety of manufacturers today, a variety of individuals in the academic community, to help define the limitations of a new system initially.

I feel that the FDA documents requiring certain limitations on very major and major errors really helps to prevent systems from getting on the market that don't meet these criteria. The predictor panel helps to identify what problems exist and how to solve those problems. It also gives us the mechanism for constant updating of any susceptibility test system as new resistances are encountered.

This is something that is done on an ongoing process. The microorganisms and new resistance is ongoing so we must, too.

Thank you very much. I will be happy to answer any questions you might have.

DR. CHARACHE: I wonder if you could put up the next to the last overhead. I would like to ask, Christine; clearly, this is the exact issue, of course, that I was asking about earlier which is how to avoid the errors to begin with. It is clear if we look at that current column that the inducible cephalosporinases did very badly, that those, or antibiotic organism combinations, miscalled almost

at

1 in 5.

They would call them susceptible when they were really resistant. This is an accentuated problem in the rapid methodology where you don't have time to induce the beta-lactamases.

My question is, clearly, the current FDA guidance does not highlight your ability to detect these in its current format. I am wondering how one can insure that if the rapids are downgraded in their level of review that these issues will be addressed.

DR. C.C. SANDERS: I think there are different levels of answers to your question. First, these problems happen for two reasons. Number one, many of these drugs, not only with rapid devices but with conventional devices, were developed before the current guidelines were in effect. That was 1991.

These are mid-1980-developed drugs. So the 1.5 percent very major error rate and the requirement for certain numbers of resistant strains were not there at the time that this was being developed. So that is one of the reasons why this happened.

Secondly, as I pointed out, new forms of resistance emerge, even since 1991, and so we have to be ever vigilant to catch them and make sure devices keep up to

at

date with them. I think that it is very clear that the manufacturers are aware of this problem and they start doing something about it as soon as they become aware of it.

There is no way we can write a document that will prevent new forms of resistances from occurring that our devices will pick up. That is an issue just for staying watchful. The issue now, with the current documents, whether it is a PMA or 510(k), the performance is the same, the performance requirement, so it doesn't matter as long as you stick to the 1.5 percent limit on very major errors.

I think this shows you that even drugs that were developed prior to that limitation being placed on very major error rates and then being calculated correctly, I might add, that we are beginning to solve those problems.

I think that that is a very positive step in the right direction but I don't think a PMA versus a 510(k) is going to impact this at all. It didn't cause it and it is not going to solve it.

DR. THRUPP: Chris, could I ask just as a ballpark question, Vitek has been very successful in jiggling, or whatever is done, to end up with excellent agreement; that is, very few or very major errors, particularly.

Just as a kind of background general comment, you could adjust media. You could adjust concentrations in the

at

wells. You could adjust the incubation time and you could adjust the computer algorithms. These are just four that occur quickly to me, in terms of how to fix it.

Roughly, how many of these were fixed by extending the incubation time so it might have not necessarily still been that rapid as opposed to how many did they adjust concentrations in general?

DR. C.C. SANDERS: I would say that if you just extended the time of incubation, you are going to fix about 60 percent of these errors. Some of our overnights have the same problem. So you will fix some of them. But then, if you take that approach, you lose the clinical advantages of giving an answer faster, which Gene will address in a minute.

The fact that we don't have to extend the incubation time but can jiggle other components to get the right answer fast is, to me, a major advance because there was a time when I thought, "We are just going to have to extend the incubation period."

Sometimes, with some organism/drug combinations, that is the only way to get the right answer. But, happily, with many of them, more than I thought at the get-go, we are able to actually adjust the parameters of the test and get the right answer but get it faster.

at

MS. GERST: What we did in a big way with these studies was to add additional strains, in fact. When we do add additional strains, then we have more data in our database to refigure the regression coefficients so that we do, in fact, change the algorithm but we are doing it not just by tweaking the line but by adding additional datapoints to the database.

DR. THRUPP: Any other questions for Dr. Sanders?  
Thank you, Chris.

The lesser half of the Sanders team, Dr. Gene Sanders.

DR. CHARACHE: That is a sexist remark.

DR. W.E. SANDERS: But true, nonetheless.

### **Clinical Significance**

DR. W.E. SANDERS: I am really grateful for your willingness to listen to me this morning. My assignment is to deal with three questions.

[Slide.]

The first; are susceptibility tests clinically relevant in general? Secondly, if they are relevant, what are the relative merits of the more rapid tests, first for the patient and then for environment and, if you will, for society? Thirdly, if rapid tests have merit, will they be used by clinicians?

at

[Slide.]

Let's look at clinical relevance in general, first. Every study performed to date includes the caveat that many factors, in addition to in vitro susceptibility, determine the outcome of antimicrobial therapy. A few are listed here, their pharmacokinetics and pharmacodynamics depending on the status of the host defenses. The presence of obstruction, abscess or foreign body proximate to infection indicates surgery is the major hallmark for affecting an appropriate outcome clinically.

We are all aware of the problems of emergence of resistance. These factors collectively sort of account for the apparent fallibility of our susceptibility tests from time to time.

[Slide.]

There has been at least one review per decade devoted to the clinical relevance of susceptibility tests. The conclusions of these, and nearly all of the hundreds of individual studies, are remarkably similar; namely, if the test result indicates resistance, therapy will fail somewhere between 80 and 97 percent of the time.

On the other hand, if the test indicates sensitivity, there is no guarantee of a favorable outcome with success rates ranging from 60 to 80 percent. But the

at

bottom line is that we, most of us in that room, continue to use these tests. And their use has recently become the FDA and IDSA published standards of practice in serious infections such as bacteremia. We all agree, I think, they are here to stay.

[Slide.]

Turning to our second question, the rationale for more rapid tests arises, in part, from the observation of points of irreversibility in infection, points beyond which even the most appropriate antimicrobial therapy will have no impact on the outcome of many serious infections.

Perhaps the best studied of these has been pneumococcal pneumonia, but the evidence is compelling for each of the entities listed there.

[Slide.]

A number of recent publications have cited the critical importance of the earliest possible initiation of appropriate therapy. I have selected here the more recent reviews that will permit you to get back to the original literature promptly, appropriate for bacteremia, sepsis, infections in neutropenia and in meningitis. The case is most convincing with bacteremia, meningitis and infections in neutropenics.

[Slide.]

at

Next, Doern and colleagues prospectively assessed the potential value of a rapid versus conventional test. You should have this among your materials provided. The microscan was compared to a broth microdilution assay for testing of the organisms listed; Staphylococci, Acinetobacter and Enterobacteriaceae. There was no difference in over 100 demographic descriptors between the two groups that were compared.

[Slide.]

The results of this were really striking to me. Although there was no difference in length of hospital stays, mortality was significantly lower when the rapid test was used. The figures there are overall mortality. Attributable mortality was 7.0 percent with the rapid method and 12.7 percent with the conventional method.

Both of those were statistically significant. In addition, patients in the rapid-test group had significantly fewer laboratory studies performed, imaging procedures, days intubated or days in intensive or intermediate care. There was also a shorter time to necessary alternations in empiric therapy with the rapid test.

[Slide.]

Often overlooked potential benefits from rapid tests are what I refer to as societal or environmental

at

impacts. It has become increasingly apparent that there is a direct correlation between the tonnage of antibiotic administered in a given location and the rate and extent of emergence of resistance.

Despite the classic study from Johns Hopkins in the 1950s that showed a 1:1 direct-line correlation between the grams of neomycin prescribed in the hospital and the emergence of aminoglycoside resistance in *Staphylococcus aureus*, medicine continues to ignore history.

Unfortunately, Nebraska is a microcosm. In our transplantation and hematology/oncology units, exclusive use of advanced-generation cephalosporins is done for empiric treatment of severe or life-threatening infections. This was followed by outbreaks of multiply resistant *Enterobacters* and multiply resistant *Pseudomonas*.

So then it was decided something must be better. We will use fluoroquinolones. They were substituted and up popped viridans streptococcal bacteremias and a host of resistant staphylococci infections. So something needed to be done.

Carbepenems with vancomycin were used for empiric therapy to cover all of the preceding. This was followed immediately by *Stenotrophomonas* and resistant *Pseudomonas aeruginosa* outbreaks. We have also had three clonal

at

outbreaks of vancomycin-resistant enterococcal disease.

The converse, I guess, of overuse is restriction. I think it has been demonstrated amply in repeated studies this nearly always diminished prevalence of resistance. Clearly, rapid tests could diminish the quantity of big guns used and, perhaps, impact the resistance problem.

[Slide.]

Additional societal benefits include reduced costs as seen in the Doern study and, possibly, earlier isolation or cohorting as indicated in the presence of multiple drug resistance.

[Slide.]

Finally, we come to the question will rapid tests be used. Our experience and that of others has been that test results are used most often when the clinical outcome is in doubt. Usage dramatically diminishes as the patient improves. Physicians are reluctant to change to less expensive, less toxic, narrower-spectrum therapy if the patient is doing well clinically.

As a consequence, we see ampicillin-sensitive E. coli infections treated for two weeks or more with ceftazidime plus an aminoglycoside often plus or minus vancomycin. This is what I refer to as "Don't get off the winning horse" mentality. The patient is doing well, why

at

should I change.

But I do sense a changing mentality. More, but probably not a majority yet of physicians are concerned about resistance and I think many wish to be a part of the solution. As an example, our chief of transplant surgery invited us to dinner at a local French restaurant in Omaha and he began the session for the evening by volunteering to suspend use of all antibiotics in the unit if it would slow the soaring rates of emerging resistance.

Can you imagine my response? I felt like giving him a hug, and I did.

On the other hand, many in medicine do remain unconvinced. I think we, academe, industry and government must become effective educators. I think the time is ripe for change and I would like to see us go shoulder to shoulder to meet this challenge.

Thank you for your attention. Questions?

DR. THRUPP: Your chief of transplant services is not innovative. There was a paper 20 years ago plus, maybe 30 years ago, in The Lancet where a neurosurgery unit in the U.K. had a Klebsiella outbreak and they didn't cure it until they eliminated the use of any antibiotic in that unit. So there is precedence for that, actually.

DR. W.E. SANDERS: Thank you, Dr. Thrupp. That is

at

really a classic.

DR. EDELSTEIN: I would like to make one comment regarding your comments on the Doern study. In fact, while it is referred to in the title of the paper as rapid in vitro susceptibility testing, it was actually a trial of rapid reporting because the method used for susceptibility testing was the same in both arms of the study, contrary to what you presented in your presentation.

DR. W.E. SANDERS: Wasn't one the microscan versus a broth-dilution assay?

DR. EDELSTEIN: No.

DR. W.E. SANDERS: I thought it was two different tests.

DR. EDELSTEIN: No; it just differed in terms of the time when the organisms were set up in the laboratory. The rapid group was set up in the morning and the conversation group was set up in the evening.

DR. CHARACHE: I would take our head of transplantation to a French restaurant if I thought it would work.

DR. W.E. SANDERS: Thank you.

DR. THRUPP: We will come back to Ross Mulder to summarize the foregoing.

#### **Summary of Discussions and Petition**

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

at

MR. MULDER: I would like to thank everybody for their excellent presentations today. In closing, I would just like to emphasize a couple of points.

[Slide.]

The historical basis for retaining fully automated, short-term incubation-type antimicrobial susceptibility devices into class III no longer applies. The state of the art of these devices has sufficiently advanced to satisfactorily address the historical concerns.

[Slide.]

Secondly, fully automated short-term antimicrobial susceptibility devices are subject to the same rigorous validation testing and FDA evaluation as other non-short-term incubation cycle devices. These other devices were reclassified over 13 years ago.

[Slide.]

FDA and NCCLS guidance documents are both well established and widely used by antimicrobial susceptibility device sponsors for validation testing. The documents complement each other and can serve as the basis for class II special controls necessary for reclassification.

[Slide.]

Even with the recent improvements in FDA review time, PMA processing requirements for short-term incubation

at

cycle types antimicrobial susceptibility devices discourage rapid application of incremental technological innovations in the U.S. Benefits of such improvements are often realized first by non-U.S. laboratory facilities.

[Slide.]

Providing rapid and accurate susceptibility results can be a critical factor in patient management situations, thus short-term incubation cycle antimicrobial susceptibility devices fulfill a critical medical need.

[Slide.]

Reclassification to class II controls resulting in 510(k) reviews will not compromise FDA's ability to conduct rigorous safety and effectiveness evaluations of new or modified short-term incubation cycle antimicrobial susceptibility devices. These devices will still be subject to the same kind of validation testing as it is conducted under the PMA process.

I think that this is an important point.

Downclassifying these won't change the way that they are looked at. The technical information that the FDA looks at will remain the same. This is an important point.

[Slide.]

Finally, reclassification of short-term incubation cycle antimicrobial susceptibility devices is consistent

at

with recent FDA reengineering efforts initiated to streamline the review of innovative in vitro diagnostics without sacrifice of scientific scrutiny. These are the FDA's recent reclassification of serum tumor markers from class III to class II.

We, therefore, believe that is contrary to the interest of public health to keep manufacturers and the FDA locked into an unnecessarily cumbersome and lengthy process to demonstrate the safety and effectiveness and implement modifications to short-term incubation cycle systems.

Moving short-term incubation cycle systems from class III to class II will offer a thorough yet rapid review of process this benefitting all parties involved, the FDA, patient, hospital laboratories and manufacturers.

I will entertain any questions now and I would like to thank you for allowing us to present to you today.

DR. ZABRANSKY: A semantic issue. We are using the term here short-term incubation, STIC or whatever acronym we love to use in the federal government. We have also used the term fully automated. I don't think that your current device that is currently marketed in the United States is really, by my definition, fully automated.

It may be more automated, let's say, then two or three of the other instrumented systems on the market. I am

at

aware that you probably have a newer one coming along that is even more automated than this, more fully automated. This is not for you. It is more for the FDA. Which terminology are we going to be using here; short-term incubation or the automated approach, because there is a distinction.

We could have an automated system that is a greater-than-16-hour approach. This is strictly semantics.

DR. CHARACHE: They exist.

DR. ZABRANSKY: And they do exist. Thank you.

DR. POOLE: The FDA will use in the reclassification petition and the letter whichever language the sponsor submitted to us.

DR. ZABRANSKY: So you are going to go along with what the company is asking the title of the group to be.

DR. POOLE: And they will further describe the system.

DR. GUTMAN: But you are more than welcome to make suggestions, changes in the semantics, if you have a preference.

DR. ZABRANSKY: It is not a preference. There is a distinct difference.

DR. THRUPP: The specific point, back to the current issue under consideration, is that the term "fully

at

automated" is linked with STIC; isn't that correct--in the petition?

DR. GUTMAN: Right. That was like as to how it was left in the class III. That was the actual definition of the systems left in the class III.

DR. THRUPP: So it is not clear whether the reason for its having been left in III was because of the fully automated aspect or because of the STIC aspect.

DR. CHARACHE: It is the STIC.

DR. THRUPP: It was the STIC rather than the fully automated.

Ron, is this enough of concern to you--this is getting premature, I guess--but that you would feel more comfortable if semi-automated or some other term were used to be more accurate with what actually there is still a little of non-automated component to this.

DR. ZABRANSKY: Or the term "instrumented" would be more appropriated.

DR. THRUPP: You can bring this up later as a suggestion, perhaps.

DR. CHARACHE: I was just going to say "instrumented" has a problem. The Steers replicator is an instrument.

DR. THRUPP: Do we have any other questions?

at

DR. WEINSTEIN: Ross, and Lauri correct me if this is not the right time for this question, but one of the issues you have raised is that there are alternative guidance documents available. One of them that has been alluded to is the M23 document from NCCLS which, as I understand it, is more designed toward pharmaceutical manufacturers in developing their susceptibility test breakpoints.

The question I have is is that document, in its current form, adequate to provide guidance for the manufacturers of diagnostic products such as yours and the development of those new products.

MR. MULDER: It is a help, but it is not what we use for--and it is not designed for that use. We can gather information from it, protocols, but it is not in use. We really don't rely much on that document at all.

DR. THRUPP: I think we would like to take time for a five-minute break and then we will resume with Dr. Gutman's presentation.

[Break.]

DR. THRUPP: Dr. Gutman from the FDA is going to answer all our problems.

## **FDA Presentation**

### **Introduction**

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

at

DR. GUTMAN: That is not true. I am going to try and provide some context for your decision making.

The topic for our meeting today is discussion and review of a sponsor-directed reclassification petition for a rapid automated susceptibility system. This is a particular interesting time to be considering such a request because the Center for Devices and Radiologic Health is in the midst of an intense period of introspection and is undergoing two active processes, one of internal reengineering and a second of responding to the external demands of our new Modernization Act.

Both processes share two important common objectives; refining our risk-based approach to the review process and finding better ways of doing business.

Reclassification of devices is a central theme in both the reengineering and the reform programs. Although the scope of changes being entertained in this program is unusual, the idea of classification has been of considerable interest to our division over the past three years as we have watched the classification system evolve or, perhaps, in some cases, fail to evolve since it was first established during the late 1970s and the early 1980s by panels such as yours.

As the panel already knows from its training, FDA

at

historically divides the world of devices into three classes, based on risks, familiarity, links to preamendment devices and an analysis of issues of safety and effectiveness likely to be raised in the use of the device.

The product under discussion today is one being considered or petitioned to move from class III to class II status. The nature of this type of change is muted, as the sponsor has pointed out, to a certain extent by the remarkable changes in our review processes which have occurred over the past five years.

As a result of these changes, we have developed a contingency-based review system which provides manufacturers with questions and data requirements appropriate for their products and intended uses regardless of their classification status.

As a result, in our division, we now quite regularly review 510(k) submissions for class II products with the same or more scientific scrutiny than that applied to some PMA submissions for class III products. Whatever the type of submission or the color of the review jacket--it happens that PMAs come in orange jackets and 510(k)s in blue jackets--we try to posit, we ask the right scientific questions, for the issues at hand.

A downclassification of a product can reduce our

at

scientific review thresholds but this is, in fact, not an automatic corollary to this process. A change from a class III to a class II product does produce other changes however, besides those which might be encountered in premarket review.

First, although almost all class III and class II products are subject to identical manufacturing requirements which now require conformance to quality systems and to design controls, automatic pre-approval inspection of these systems is reserved for class III products.

It is possible, however, I might point out, for the division to obtain GMP inspections in association with clearing particular class II products, but this does require a special request to our Office of Compliance and prioritization of inspection activities by that office.

Second, class III products, unlike class II products, are required to file annual reports indicating problems, changes and providing a literature update on the device.

I would point out that in the previous discussion, a question was raised about how new limitations would be handled for newly discovered resistant organisms and that would be in a PMA automatically required. In the 510(k), it would not automatically be required although that could

at

easily be built into the special control by anyone who might recommend it or by anyone who might be willing to craft an additional sentence or two to make that part of the special control.

Third, the time requirements required to be met by the agency differ significantly. Our goal is to review class III products in 180 days. We, frankly, hope to do better but the goal is 180 days. Our goal for class II products is 90 days. We hope to do better. Our goal is 90 days.

Finally, the administrative and paper trail for class III products, although a target of refinement and reengineering, remains considerably more complex for both us and the sponsors than is true for a class II product.

The Division approaches the issue of today's classification with an open mind. We hope that we will frame the right issues and questions to help you arrive at a reflective recommendation for us to use in fostering good regulatory science and a balanced regulatory program.

DR. THRUPP: Do the panel members have any questions for Dr. Gutman?

DR. CHARACHE: Again, in the interest of not requiring anything that is not productive, let me ask how productive or valuable you have found the elements to be in

at

the level III that would not be there unless we specially asked for them, specifically the manufacturing requirement issue, not only for this particular product but for any of the predicate products that would come in. How important would that be?

DR. GUTMAN: We actually think the GMP is pretty important. It is important whether it is a class III and it is important whether it is a class II. It differs in importance depending on how familiar the technology is.

One of the subjects of the reengineering process, and I believe in truth in labeling so there is a lot of curiosity and ambivalence and concern and excitement and all of the above about the reengineering process, but one of the notions of the reengineering process is that it might affect the way we look at GMP, the way we handle that program, that we have a program in place that has incredible potential if it is correctly realized and it has less incredible potential if it is not correctly realized that is design controls.

It is really hard to know, in the midst of this process, how it will all sort out. But I would never sell GMP short. From my perspective, the need for GMPs should not require this to be a class III versus a class II.

What it should require is that if you really

at

strongly feel it is necessary or we feel it is necessary, we ought to incorporate it as part of the class II special control. The concept here is whether and when in the process--there are some folks in the division--I won't mention any names but I happen to be one--who think that a more interesting time to look at GMP is six months after they have scaled up rather than before they have started to make a product.

DR. CHARACHE: May I ask the same question of your other several points? Specifically, how important is the extra 90 days in terms of insuring a good validation review?

DR. GUTMAN: It is an interesting tradeoff because one of the concerns is to lock ourselves into 90 days, which is short time frame. We did benefit from this because some of the administrative trappings of the PMA--I don't know how to phrase this kindly--let's just say can be onerous and interesting.

So it is with ambivalence. The two processes are starting to converge because we are playing around in the division and probably have not widely talked to our panels about it because it is so preliminary and we probably should, we certainly have communicated to the industries that we are playing around with what we are calling a streamlined PMA and trying to actually make 120-day PMA

at

times for products where there is well-developed guidance, where there is well-developed technology, where the disease is well understood.

If this were not to be changed to a class II product, this would probably be a perfect product to consider for streamlined PMAs because this is, whatever else you can say about the product--we are going to ask the questions. I don't wish to take Liz's questions away from her.

We know about this after it has been on the market and we know its beauty and we also know its banes and blemishes.

DR. CHARACHE: Can one get rid of a lot of the paper multiplication without switching designation? In any event, can you streamline paper?

DR. GUTMAN: We are going to try.

DR. THRUPP: Along the same lines, not necessarily with this product, but when this become a generic switch, if you will, from class III to class II, are there examples, in your past experience where No. 2 on your list, the annual reports, which would no longer be coming in, might have picked up problems in other devices, whatever, that you would have wished you could have had and might have saved some problems in patients.

at

DR. GUTMAN: I think it is certainly is theoretically possible. I don't know how often it occurs. Our scientists in the Microbiology Branch read the literature intently. They are on the Internet all the time, and one would guess a really significant problem might be picked up long before it appears in an annual report or gets buried in an annual report.

It is certainly theoretically possible that interest in information might appear that we had missed somehow. But it won't have appeared in JCM or on the Internet or any very highly visible form.

We are trying to do a better job in reengineering in terms of finding out ways to communicate problems faster than an annual report. I don't know if we will be successful in doing that, but that would be a goal of reengineering.

DR. THRUPP: I hate to throw in another little caveat but, with the budget cuts, will you be able to afford to send as many of your people to the ASM to keep up with things as you would like?

DR. GUTMAN: No; we won't. So the people who go will have to teach us all. That is a very good question. Our budget cuts are very significant and are matters of concern to our scientists and our management.

at

DR. THRUPP: Any other questions for Dr. Gutman, because we don't want to shortchange--Elizabeth Rogers?

**Summary of FDA Concerns**

MS. ROGERS: Good afternoon and welcome.

[Slide.]

My name it spelled wrong in the program but if that is the only thing that happens to me on Friday, the 13th, I have no complaints. There is no "d" in my name. It is as it is on the slide.

As we are all aware, one of the most important tasks of the clinical microbiology laboratory is the performance of antimicrobial susceptibility testing on significant bacterial isolates.

[Slide.]

Today, we are considering a petition to downclassify the short-term incubation cycle antimicrobial susceptibility test from class III to class II. Earlier this morning, bioMerieux Vitek presented data and information relating to downclassification of their short-term incubation cycle antimicrobial susceptibility device.

At this time, we may revisit some of that information but we will primarily look at issues that concern the FDA regarding these "rapid" systems.

at

[Slide.]

This is the indication for use that was presented to the FDA in relation to this downclassification. As stated, it says, "Vitek's indication for use states that the system is fully automated." We have already discussed that at length. "Intended for the susceptibility testing of bacterial pathogens to antimicrobial agents.

"It is based on optical detection of growth," Growth is an important word for us in the agency, "of bacterial isolates in media with selected antimicrobial concentrations during a short-term incubation cycle, again, usually less than 16 hours.

"Test results are used as an aid for the physician in making therapeutic decisions involving the administration of antimicrobial agents."

[Slide.]

On this and the next slide, we see that antimicrobial susceptibility tests, ASTs, have a long history in DCLD. In 1976, when they were originally regulated as devices, through 1978 when the Vitek AMS was first approved, to 1984 when all overnight semi-automated and automated methodologies were downclassified, to today, when we are considering this downclassification of the short-term incubation system.

at

[Slide.]

Points to consider. In this and the next slide, we note the major issues the agency considered when reviewing this petition. Yes, we all do have many years experience with susceptibility devices. Because of this, in 1984, the FDA downclassified the semi-automated and automated devices with the exception of those rapids. Again, this was brought up this morning. Again, those rapids are those that incubate at less than 16 hours.

In addition, we do use the NCCLS standards, not just M23 but whatever we need to use regarding NCCLS standards, we use. We pull out the book and we use it.

[Slide.]

Then we do have a guidance document that requires comparison to standard methods which are read after 16 to 24 hours. So both the rapids and the overnights are compared with what we consider the gold standard which is the overnight incubation, whether it is the microtiter plate or--but it is overnight incubation.

[Slide.]

But, because of limited incubation with the rapid systems, the literature acknowledges and we see more false susceptible results, false resistant results, fastidious organism problems, the ability to detect resistance, and

at

organism growth as the basis of the STICs.

That isn't a problem right now, but we did consider it looking at future technologies that may be coming in.

[Slide.]

To briefly clarify, false susceptibility is the system reports antimicrobial results as susceptible when the organism is actually resistant. Again, as was brought up this morning, that is one of our very major errors and they are only allowed 1.5.

[Slide.]

False resistance is the system reports antimicrobial results as resistant when the organism is actually sensitive.

[Slide.]

The problems with fastidious organisms. Some gram positives we know as well as some gram negatives such as Pseudomonas grow poorly with shorter growth times and the ability of a rapid system to allow for growth up to 16 hours is something that we like to consider when we are looking at rapid systems.

If the cutoff, the drug-bug tweaking or whatever, makes it cut off at 5 hours when it really should go to 10 or 12, it is nice to know that a system can do that, has the

at

ability to do that.

[Slide.]

The ability to detect resistance. We talked about this a lot this morning. We are seeing much more of this today and, as was brought up, I personally believe, also, that we are seeing a lot of it because of overuse. But the emerging heteroresistance of organisms to beta-lactam antibiotics, the inducible resistant mechanisms seen in some drug-bug combinations and the organisms that have high mutation rates.

[Slide.]

The Vitek is based on growth. Again, as I just mentioned, we do have to look into the future a little bit and other technologies may not be based on that. We do have molecular technology out there that is beating quickly at our door for various and other systems. Growth is the only basis on which susceptibility testing has been performed and evaluated to this date.

[Slide.]

In summary, the FDA acknowledges and agrees with much that has been said today. However, as presented, our concerns lie with the greater extent of problems that we see with the rapid systems especially with the detection of resistance and the availability of time to allow organisms

at

to grow before a system provides the final result.

One of the things that I do need to make clear that was brought up earlier too was that today there is no mechanism--we do not have a mechanism and no one, to my knowledge, has a mechanism of overseeing any system as far as the evolution of resistance.

We basically rely on the literature, on MDA reports, on the company and, as Dr. Gutman says, very often we find it in the literature first. Those who really know how to surf the net probably find it there first.

So I am just going to put up the questions quickly. Then we can handle them. These are the three questions that we have for the panel.

[Slide.]

"Are you aware of any other risks or benefits to health presented by the use of this device that were not mentioned by the manufacturer in this petition?"

[Slide.]

"Does the FDA document review criteria for the assessment of antimicrobial susceptibility devices," and I think you all had that in your packet, "and the NCCLS standards," and, as I said, we use them all, "provide sufficient information and guidance to assure the safety and effectiveness of this short-term incubation system if it is

at

reclassified."

These are live documents. The NCCLS standards are renewed, always updated. Our guidance document is the same thing. It will be a live document. It is a document that can be worked on and will be worked on over time.

DR. CHARACHE: I think the point that Mel made earlier is that none of the NCCLS documents quoted apply to the rapid test.

MS. ROGERS: Right. But we use any and all. We use those as far as guidance for susceptibility--but we don't just use the M23. We use anything that we feel can help us in looking at them even as far as the media.

[Slide.]

The last question is, "Are there other methods available to review data to permit assessment of the safety and effectiveness of the short-term incubation cycles as a class II?"

If you like, Sally will put all three of them up together--after lunch? Oh; all right. After lunch. Any questions?

DR. THRUPP: We are right on time. If there are some questions while the presentation is fresh in mind? Are there any other questions that come to mind right now?

MS. ROGERS: It is always good to be before lunch

at

because the stomach usually speaks louder than the brain.

DR. THRUPP: That's right. We are adjourned for lunch.

MS. ROGERS: Thank you all very much.

[Whereupon, at 12:30 p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

at

A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

DR. THRUPP: Let's resume the session. We have been presented with the questions, the nitty-gritty three questions, which the FDA has presented for the panel. We might as well leave those on the board as a reminder, but let's go on to the open public hearing section of this meeting when anybody who is in attendance who has indicated an interest may make a presentation.

We have one listed by Sharon Cullen from MicroScan.

**Open Public Hearing**

MS. CULLEN: Thank you. My name is Sharon Cullen. I am the Director of Regulatory Affairs for Dade MicroScan. On behalf of Dade MicroScan, I would like to thank you for the opportunity to address the topic of reclassification of rapid susceptibility devices.

[Slide.]

First of all, I would like to focus my comments on two areas. Dade MicroScan supports the reclassification of rapid susceptibility devices from class III to class II. Secondly, as part of the implementation of this reclassification, revisions should also be made to the review criteria for susceptibility devices.

at

[Slide.]

The types of special controls have already been discussed by several parties during this morning's meeting. Dr. Sanders has indicated that challenge sets of resistant strains are key to evaluating the ability of different systems to detect resistance. CDC has provided several such sets of strains.

For example, gram-positive and gram-negative challenge sets have been available since the early 1990s. In addition, in order to address emerging resistance, enterococci and pneumococci challenge sets were added in 1994.

The FDA requires that for all manufacturers during either their PMA or 510(k) submissions, that these challenge sets be tested and the data included in the submission. In order, also, to address the question of internal challenge sets and what do we, as manufacturers, do to continually evaluate that, we take these challenge sets and we, as JoAnna had indicated, evaluate our system's performance early within the development process.

We also take resistant strains that have been identified and sent to us by our users and we also purposely go and we collect resistant strains from different individuals within the scientific community such as Dr.

at

Sanders, such as Courvalin. Several of our international sites also send us resistant strains.

We include those within our internal databases and really challenge our systems before they even get out to the clinical trials. These systems, these challenge sets, can also be utilized to monitor performance of the systems after release.

[Slide.]

MicroScan has the unique experience of having multiple classifications for a single device. MicroScan's Walkaway instrument is a fully automated system that is used to read overnight susceptibility panels. That is regulated under the 510(k) process. Our rapid panels are regulated through PMA submissions.

I can tell you from experience that the scientific scrutiny, both internally and externally, is the same for both. Our processes, both in monitoring manufacturing and in monitoring customer complaints, in monitoring the evaluations that are done throughout the world, are the same.

We work closely with the scientific community to evaluate the performance. We utilize some of these new sets of predictor panels, as Dr. Sanders had described, to evaluate our performance. In fact, we presented at an ASM

at

late-breaker session one of the first vancomycin intermediate Staph aureus strains and did this in conjunction with the CDC.

So, also, in answer to the question of what do we do continually work with the scientific community and then work with our products to improve performance, we work closely with the CDC and with our customers in getting these strains in, evaluating performance and, where possible, going ahead and implementing improvements.

The 510(k) process would allow us to implement these improvements a lot quicker and be a lot more flexible in our ability to do that.

[Slide.]

Also, there was some discussion about fully automated versus rapid susceptibility. FDA has evaluated a rapid susceptibility device and this one was evaluated as a 510(k). This is a manual system that detects oxacillin susceptibility or resistance and the reports are available in four hours.

[Slide.]

In summary, the requirements for the various susceptibility systems are not consistent. There is a PMA for the rapids, the 510(k)s for overnight--

DR. THRUPP: I'm sorry. Before that other side

at

disappears, you are right; this is a rapid method.

MS. CULLEN: Yes; it is.

DR. THRUPP: It has not been discussed so far today as one that already is on the market as a rapid method. Was that downgraded, or reclassified is a better word, to a class II or did it stay as a class III and was given a 510(k) procedure?

MS. CULLEN: I can't speak to that.

DR. THRUPP: Can someone answer?

DR. GUTMAN: We are caught off guard. To our best recollection, it was because we didn't view this, actually, as an MIC system. We viewed this--rather than using semi-quantitative information, we viewed this as being nominal information. This was a single bug and it was a non-automated system, so there were a number of factors which produced what, frankly, in looking at it now, may be a slight inconsistency. But there were reasons for that inconsistency.

DR. THRUPP: But, in essence, it was a class II. It was made class II.

MS. CULLEN: Which brings me to my next slide is that there really are inconsistencies and it is confusing with the classification of susceptibility devices.

DR. GUTMAN: We can fix them in either direction.

at

[Slide.]

MS. CULLEN: Another such example is disk-diffusion. A labeling review is the premise for the disk-diffusion submissions, and even disk diffusion has significant performance limitations. As Dr. Sanders had indicated, all methods have some limitations. The important thing is to know what they are and to address them within the labeling. The special controls that we have discussed really are adequate for that.

[Slide.]

My second point is, to implement the reclassification, revisions should also be made to the review criteria for susceptibility devices. Minimally, the reference to the PMAs and rapid susceptibilities are included in the current 1991 draft of the FDA review criteria.

[Slide.]

In addition, it could also be an opportunity to evaluate the study requirements for these and make them more consistent. As Dr. Sanders had indicated, the important or the key point to detecting resistance really is in the challenge set of strains and not in collecting large numbers of susceptible strains. That is the primary difference between the two from a data point of view.

at

[Slide.]

In addition, there has been a lot of discussion on very major error rates. The NCCLS, in some of the recent discussions on M-23, has recognized the value of using resistant strains to calculate the very major error rates. This was incorporated several years ago into the FDA review criteria.

However, one of the questions is, within some of the discussions in comparing methods, is 1.5 percent realistic. Can it be achievable? When you compare MICs with Kirby-Bauers, there are instances where the error rate is greater than 1.5. So it may be an opportunity to take a look at this as well.

But I do agree with the comments of looking at resistant strains as the best way to do this. So what should that number be?

[Slide.]

In conclusion, Dade MicroScan supports the reclassification of rapid susceptibility devices from a class III to the a class II. We believe that the AST review criteria should also be revised to reflect this. This revision could be done, and should be done, concurrent with the classification. The joint manufacturers could play a role, a primary role if the FDA would like, in the efforts

at

to revise this guidance document.

We have worked together in the past in collecting and compiling some clarifications and improvements to this document and would be happy to assist the agency in coming to a joint agreement on what this could and should be.

Thank you.

DR. THRUPP: Thank you, Sharon.

While Sharon is at the podium, does the panel have any questions of Sharon? Everybody is uncharacteristically silent. Then, can we open the floor from any other comments from the audience.

Nobody else wishes to make a comment, so let's go right on to the open discussion.

#### **Open Committee Discussion**

DR. THRUPP: We would want to be addressing the questions. Maybe we could put the three questions back up on the board. "Are you aware of any other known risks or benefits to health presented by the use of this device that were not mentioned by the manufacturer in this petition?"

Can we open that for discussion?

DR. CHARACHE: I think that I am separating the question of some of the scientific reviews that we have heard from what it says here which is the petition, itself, because I think there are some points made in the petition

at

that I would love to see modified so that it didn't look as though any change that we might favor was based on some aspects of the petition which we wouldn't want to see used as a precedent elsewhere.

Now, to address this first question of the uses that were not mentioned by the manufacturer, I think the point is made in the FDA guidance--is it guidance or--guidance document that if an organism is found to be resistant, it generally will not work in the patient.

That point was made also by Dr. Sanders. Depending on the patient base, 80 percent to 97 percent of the time, you will be using a drug which is not efficacious.

I think some of the points that were made in the clarifications of the petition emphasized a whole range of factors which can affect whether an in vitro test will be accurate or not. All of those factors pertain to an organism that is considered sensitive.

I think the key thing to emphasize is that the reason for doing this test is to find resistant organisms as our number-one, major requirement. Because that does represent a very substantive risk to patients, I think that point should be clear in the petition, that we are really looking for resistant strains and that it is a real threat to the patient if these are not identified.

at

So I think that would be an aspect of risk to health that I would want to see emphasized. That is independent of whether we think it is a good idea to change strategies.

There are some other aspects of the petition. I don't know if you would want them addressed now or not that I would want to see--

DR. THRUPP: This is the only point in the questioning where the petition is mentioned. I am not sure whether each aspect of the petition is critical to decision-making, but in terms of giving a gestalt for how these may be received and how the FDA may respond, it seems to me that it would be appropriate to have comments about what is in the petition.

DR. CHARACHE: I will make a few others, then. I think it is important to note that one of the reasons for feeling that the petition should be approved is because there are guidance standards. There are four guidance standards named. The M-2 document and the M-7 are very useful in providing the backup control for the test but they don't speak in terms of the media, the inoculum and all the rest of it. They don't speak at all to the rapid testing.

The M-23, as was pointed out, also does not. It speaks to how a drug manufacturer sets the window for what

at

of his antibiotics should be considered. Where it can provide guidance is in issues such as the number of reference laboratories, or clinical laboratories, that should be used for testing. That number is six. Here the FDA guideline is either two or three, depending if it is a 510(k) or a PMA. So that is not being followed.

So it really isn't a guidance for this purpose. I don't think we should say there are guidances that don't exist. When we look at the FDA guidance document, I wanted to see how that was being applied now. So I did ask if I could see the most recent cephalosporin, the document for the clinical trials that were used for that, the three laboratories to which they went.

This information was provided. I have reviewed, just a few minutes ago, earlier after they spoke, with Ross Mulder and JoAnna Gerst, that this, in fact, was the appropriate document which had been sent by bioMerieux Vitek.

It doesn't follow the FDA required guidelines. They require that one do ten resistant strains of *Citrobacter freundii* and I think there are three, and not tested by every laboratory. The extended beta-lactamase organisms were not tested.

So, in fact, the documents which the petition says

at

will serve are not serving. I think that should be either clarified or removed from the petition.

Also, in the petition, it notes that there is no problem because, in 20 years, physicians had not complained about faulty susceptibility testing. I would strongly urge that that be removed. I think our most concrete example of this was the vancomycin-resistant enterococci.

When CDC had 25 strains and no doctors were complaining about it, Hopkins had 140 strains. We knew they existed because our susceptibility test method happened to pick them up whereas the automated systems and Kirby-Bauer did not. But were there complaints from the doctors all over the country because people were dying of these or the ESBLs? The answer is no.

There is no way a physician can pick up the error. And that is a risk that should be stated. They can't tell. If the patient fails to respond, they don't know whether it is because the site of pathology or the severity of illness and all these other factors that affect whether a susceptible strain will or will not respond.

So I think that should be reexamined. I certainly would reexamine the association of tumor markers in terms of severity and risk and placement compared to rapid antibiotic susceptibility testing. It is a non sequitur and, if it

at

helps at all, I just came, week before last, from a meeting of CLIAC in which the HCFA is reconsidering what one should do with some of the genetic tumor markers and suggesting that, perhaps, our current regs are not strong enough.

So I think from two directions, first because it doesn't apply to the severity of the risk that can occur for failure to address a resistant organism and, secondly, because it may or may not require or be upgraded in the future. I don't think that should be part of it.

So I think there are a number of things that trouble me because I have, by no means, decided whether the class should change. But I would hate, since our charge was to look at the petition and decided, based on that and these criteria, whether it would be changed--I would had to change it based on this particular petition without a modification or review of some of these factors which are in here.

DR. THRUPP: Do we have any other suggestions or comments? I have one kind of with my editorial hat on. Oh; Paul?

DR. EDELSTEIN: I agree with some of Dr. Charache's comments, but I would like to say that the petition specifically says that the manufacturer is unaware of any reports of human adverse experiences. That is different than physician complaints, which you highlighted.

at

DR. CHARACHE: Oh; it has both in here. I will find it for you.

DR. THRUPP: It does use the word "reports," but I must confess that I am sympathetic to Dr. Charache's points. I circled some similar ones that the implied context, the way it is used, implies that the result is not such a big deal or people would have had more problems with it. I am not sure that that is the message that we want to have a petition convey.

DR. CHARACHE: There is one additional risk that I wanted to put on the table. On page 22, there are six unfavorable points which the petitioners point out to us. Then, on page 23, it addresses them.

But, in five of the six cases, the way to avoid the false report of susceptibility was to pay attention to the inoculum size including the suggestion that nephelometry be used to insure the appropriate inoculum size to avoid calling the resistant organisms susceptible. I think, with that type of recommendation as the resolution, we really should understand whether nephelometry is the standard of practice in the community or how inoculum size is proposed to be controlled.

That is, again, just reading the petition.

DR. THRUPP: Dr. Zabransky?

at

DR. ZABRANSKY: I will reserve my question. It has to do more with question No. 2.

DR. GATES: I think we might agree that those are legitimate points, but I don't know that it is particularly applicable to whether it gets downclassified to III or II in the sense that we have all agreed that whatever the performance criteria turn out to be, they should be used in the same case for either a II or a III.

DR. CHARACHE: I hope I made it clear that I think that the issue I would like to see addressed is the fact that we are to decide, based on the petition, whether that should be done. I would not like to see this petition setting a criterion for future action along the way besides.

DR. THRUPP: What Dr. Charache indicated is true. She raises one very valid point that does speak to the issue of why should rapid tests be treated, or should they be treated, any differently in the review process than the standard overnight; namely, a number of these references come down to the fact that inoculum size seems to be more critical for an accurate or a valid result with the rapid tests than it does with the standard.

So that could be an issue which the FDA and the committee could take into account. In terms of evaluating a decision, is there any added potential risk for the rapid

at

method, whether it should be class II or class III. There is a difference in the scientific data there.

DR. EDELSTEIN: Might I make a suggestion? I have a laundry list of things I would like to see included for product evaluation and use. I don't know when we would discuss that. In part, it has to do with the FDA review document and in part it has to do with what I think are needed changes to how the product is evaluated and how it is used, whether that would be a separate discussion or not.

But maybe what we could do is to confine that laundry list because I am sure other people have them as well.

DR. THRUPP: I think that is points 2 and 3 that you are getting to. That's where those comments would come in.

DR. GUTMAN: Let me interject that a decision to downclassify from III to II would come with a special control and, with all due respect to NCCLS, this would be a case where the FDA would have the final word. So our document probably would have more credence than the others which you would refer to.

Obviously, it would be important to us--frankly, it would be important to us even if we didn't downclassify this to know how we can make our document better.

at

Obviously, if we did decide to downclassify, then it is absolutely imperative that we get all the right stuff in that downclassification.

So, either way, whether you make it part of 2 or 3 or make it part of the condition of whatever you vote on, we want to hear. Again, if you think of something on the train or plane on the way home, you should call us and tell us how we can make this a better document.

DR. THRUPP: The point that Dr. Charache made about the petition and its content in terms of precedent setting, there is one just editorial-type comment that I was going to throw in. It really comes back, I think, to the inoculum size. I had a little editorial difficulty--for example, on page 23 and 24 where the sponsor has indicated a potential problem that had been raised such as No. 2.

This was the incubation period not being adequate, possibly, for expression of all resistance mechanisms and especially the inducible beta-lactamases. The concern is listed in reference No. 9 which was published in '93, presumably reasonably recent concern.

Yet the response to that concern was referring a paper back in '88 which was already readily available. So it is kind of backwards. I would have hoped that the correction would have been the most recent response.

at

Analogously, in No. 6, about oxacillin susceptibility, the reference about the concern, or the problems, was published in '92 but the response refers to a paper back in '87.

That is a little bit backwards. But I think these issues were addressed in the presentation and I am not sure that these are substantive for our decision. It is just a comment about the petition, itself.

Any other comments on question 1? Then, let's go right to question 2, "Does the FDA document review criteria for the assessment of ASDs and the NCCLS standards provide sufficient information and guidance to insure the safety and effectiveness of the short-term incubation if it is reclassified as a class II?"

DR. ZABRANSKY: This is where I would like to raise my question. I just lost the page in the guidance document. Which appendix was that? B, as in boy. There is a chart at the back of the guidance document. This is where we see some of the differences that exist between PMAs and 510(k)s, disk versus some of the other methodology.

I would like to hear some comments from the FDA as to how and why these differences for submissions--in other words, two sites versus three sites, which we heard about, and numbers of organisms--why is there this inconsistency to start with and, if we know why there was this inconsistency,

at

then we can maybe make some further recommendations.

This is page A1 under tab B.

DR. GUTMAN: The issue is that we have a sort of weak history of this. There are not too many folks here who were actually involved in those data decisions. There was some historical evolution here and we think that they have to do with--

DR. THRUPP: Freddie Poole may have an answer here.

DR. ZABRANSKY: Then there is a subsequent page which has some differences on it as well. You see the CDC challenge number of organisms and the stock organisms and then, down below, we have--and then there is another page with the Kirby-Bauer has only one site for a 510(k), et cetera.

DR. GUTMAN: Freddie has got the answer. She actually knows the history.

DR. POOLE: The reason that we required more information for the rapid systems was because of all the problems that we were not aware of at the time, and we knew that we needed more datapoints in order for some of the slow growers, some of the fastidious organisms and some of the ones that would later on either develop resistance.

So we believe we needed more datapoints for the

at

rapid system than we did for the overnight system. Then, number two, the standard reference method was an overnight system. So we thought we had more information on the standard reference method.

DR. ZABRANSKY: But the standard reference method, you are requiring more organisms there than you do for the Kirby-Bauer. This is on page A1, one site versus three sites, number of organisms, zero versus 100. That is what I am looking at is the differences--

DR. POOLE: The Kirby-Bauer was the disk. The disk, when Drugs approve their devices, they do clinical trials and they include the disk. We get the data directly from the Center for Drugs.

DR. ZABRANSKY: So you bought what was provided to the agency--

DR. POOLE: To the agency from the Center for Drugs.

DR. ZABRANSKY: Okay; now I understand. That is what I was really looking at is why is there a difference between the 510(k)s, not between the 510(k) and the PMA. That was more understandable.

DR. THRUPP: To conclude that little discussion, there is no reason why we couldn't, in view of the potential problems for inoculum, for resistant organisms and for the

at

concerns that have been expressed, part of our special conditions could be that those numbers be elevated, instead of 100, go to the 300 or whatever.

DR. CHARACHE: I would even wonder about perhaps it being practical to have more sites. In this little study that I was looking at, and I just asked for the most recent cephalosporin to look at, the percent agreement with Enterobacter and the cephalosporin vary maybe 1 percent in one lab to 100 percent in another.

I think that a few more sites even might be helpful although these were ideal labs and they were very well chosen. Maybe instead of doing all the paperwork, we could substitute some more science.

DR. THRUPP: Do you want to go to the point of making that a specific comment yet or shall we reserve those to the end because we have got a couple of specific suggestions here for modification of the guidance document.

DR. WEINSTEIN: I would like to ask Dr. Sanders, Christine Sanders, about the challenge set and what your feelings are since you are one of the founders of that concept. How do you feel about the lower number of organisms being tested?

DR. C.C. SANDERS: Are you talking about the CDC challenge set?

at

DR. WEINSTEIN: Or your set.

DR. C.C. SANDERS: Or mine or anybody's total?

DR. WEINSTEIN: The whole concept and what the right number of organisms would be to test.

DR. CHARACHE: And could you comment also on whether the CDC set is still the best one or whether we shouldn't be modifying its content.

DR. C.C. SANDERS: Okay. I will answer that question first because it is easy. The CDC challenge set is a very important set that, unfortunately, has not been kept up to date as rapidly as it should. Thus, right now, it doesn't have any strains with the SBLs in it. Quinolone-resistant Enterobacteriaceae are not there. So its major limitation right now is, number one, it is not reflective of what is really happening today but it is a great source of resistant strains that people would not necessarily have.

So, yes, it needs to be updated. It is of value and it needs to be updated more often than it is being updated. Secondly, unless they change their approach, right now, the CDC is not telling us the mechanism involved in the resistance.

They give us MICs and disk data so we know what the pattern is, but they won't tell us the mechanism. Now,

at

I happen to know on some of them because I sent them the strains. I can also look, myself, to find out what the mechanism is. I cannot publish that or disseminate that information.

So when the FDA requires certain numbers of different types of mechanisms, that is not a helpful source because we don't know the mechanism. It hasn't been divulged.

I think that these types of collections of strains, either the CDC challenge panel or panels like we have been able to put together and others have been able to put together from their stock isolates are absolutely the backbone and very important to documenting accurate detection of resistance.

What is the proper number? It is hard to say because certain bug-drug combinations, the potential for resistance isn't as great as others. Personally, the larger number, I like to see across the board--across the board, not one particular method doing less than another particular method because the strength in detecting resistance is in the number of strains you have tested, not in the intrinsic strength or weakness of the test.

So I would like to see a uniform number of those types of isolates being required regardless of type of test

at

or class III or class II. Again, there should be some give and take in the actual number looked at depending on the particular bug-drug combination.

I do know, and the manufacturers certainly know, the larger the number of these strains that they test, the better their data are. We talk about a very major error of 1.5 percent which is very difficult to achieve, sometimes impossible.

But the larger number of resistant strains that you have tested, the better and more realistic that number is. Then, with that number, you might be able to identify certain minor hot spots that are contributing to the major error and be able to disqualify that rare combination and still keep your test.

So I am all for a reasonable large number of these types of strains across the board.

DR. THRUPP: In follow up of that comment, could I ask the committee would you feel that one thing we should suggest, aside from the numbers of organisms and the numbers of sites might be that an additional challenge set, selected to test bugs with known resistance mechanisms, be included.

DR. CHARACHE: Yes; we can. It is just that it is not the CDC set. It is an expanded CDC or a second complementary set in which the mechanisms are known. I

at

would think that our colleagues would help supply it.

DR. THRUPP: It is probably realistic to expect that known strains could be derived.

DR. CHARACHE: Or that the CDC could be persuaded to provide the information.

DR. EDELSTEIN: I think that the current guidance document is methodologically and statistically flawed. It is methodologically flawed because it doesn't take into account testing strains with newer resistance mechanisms, as is obvious in what we have heard. You need a new challenge set.

So, somehow, if the document could be rewritten to specify challenge sets and include an adequate number of organisms of each resistance mechanism type, and what might have to happen is that that document would need to be updated on a frequent basis whenever a new resistance mechanism was discovered.

That might help quite a bit because if you did that sort of testing, then the numbers or organisms you might need to test might be less. The reason why I think it is statistically flawed is because it mentions acceptable rates of error but doesn't give acceptable confidence intervals of that error.

Just as an example, if you are talking about a 1

at

percent error rate, the upper limit of the 95 percent confidence interval for 100 strains tested is 5 percent. For 300 strains, it is 2.9 percent. For 500 strains, it is 2 percent.

So I think it would be much better to establish a range, an acceptable range, of errors rather than a certain number because, if, for example, on 20 strains of a particular bug-drug type that are tested, then the estimation of that error could be very huge. That would get away from the problem of specifying certain numbers of strains to be tested and would, instead, rely on something that would be more statistically valid.

These comments are reminiscent of the ad nauseam, I must say, sometimes, discussions at NCCLS meetings about how to try to fix these documents to be generically applicable when each drug has such different scenarios to come up with a generic guideline with statistical intervals.

If there are only 20 or 10 strains of VR Staph aureus, how can you expect to have a manufacturer come up with statistical variation when there are only a few strains even recognized.

DR. EDELSTEIN: Under the current document, if there are fewer than a certain number of strains and that is not listed, and it says that this method may not detect this

at

susceptibility pattern--I may be paraphrasing it--but that is going to be a continuing problem.

Simply relying on a mean number without specifying a range, I think, is a real mistake. It is misleading.

DR. THRUPP: That very point came up for much discussion at NCCLS where there was fear that if the 1.5 percent--and these could be part of suggestions to the FDA--if that 1.5 percent were applied rigidly, would it result in rejecting an otherwise reasonably good procedure because there are so few strains available that one error out of ten strains might still benefit the people and the public health and, yet, is a 10 percent error and would, therefore, be rejected, a cautionary statement or something.

We did call on Christine from the audience and there was someone else that did have their hand up. In order to expedite this--

DR. ZABRANSKY: Still sticking with the document, to follow-up what Paul said here, looking at page 1 of appendix B, we have here a document that was originally written 1990 by the FDA and I know it was submitted to a number of people on this panel for comment which we made.

We have here, in 1991, a draft document--it is still referred to as a draft document, to my knowledge, and, in addition to that, it is called here a flexible document.

at

It is really not flexible unless it is generic enough and reflects some of the things that Paul has been talking about, whether it is numbers of organisms or numbers of sites.

On the other hand, if you wrote this document and rewrote it every year, the FDA group would be doing nothing but rewriting this document and not reviewing the 510(k)s. So, again, something has to be done to make this more general.

DR. THRUPP: I think we did come to a little consensus that we could recommend that there be an addition to the A1 table, that we elevate the numbers, perhaps, to the 300 and that there be an added group of known resistant mechanism challenge organisms added to the document.

We didn't respond specifically to--I think it was Dr. Charache brought up the concern whether three sites are adequate for field testing, if you will, of a new device or a new drug.

DR. CHARACHE: Two thoughts and, perhaps, a compromise solution. It is not only, I think, the number of sites but I think it would be very helpful to consider including a community hospital site, somebody who is not an expert, to see whether these inoculum size issues appeared.

But my generic recommendation is that the entire

at

document be reviewed in concert with, perhaps, members of the panel and, certainly, industry to update all of it and not just the table. That is in line with the question of whether those four documents are adequate for the purpose. I don't think they are and I think it should be reviewed.

DR. THRUPP: I think that is a proposal that no one would disagree with, for a change, that people get together to update the document.

DR. EDELSTEIN: One thing that you could do and I would actually suggest it is to utilize these challenge sets in the field trials of the panels. That would be a true test of the performance--I don't know if it would be a true test, but it would be a better test of the performance of the product and would be, presumably, much more sensitive to errors in inoculum preparation than currently.

DR. THRUPP: Exactly. We have already addressed the issue of the challenge sets. But that does come right back to my point that we didn't address the number of sites. We could say, for the submission, three sites is okay as it was in the PMA, and ask for postmarketing of "x" number of sites.

On the other hand, you could interpret, although the goals may not be exactly parallel, some of the NCCLS documents to suggest that five or six sites--I forget what

at

the last draft was--should be used even in the developmental phase.

So I wonder, can we have another comment about the number of sites?

DR. GUTMAN: A couple of comments. Historically, three sites have been used for most clinical studies for IVDs with the notion that two out of three will agree and you will see something--there is actually nothing, as far as I know, either statistically or biologically. I have always been troubled, personally, by the use of three, whether that is too many or too few. I guess that would be a subject of interest from your perspective.

If this is maintained as a class III, we have very strong postmarketing controls. If you do downclassify it to class II, we have a potential for postmarketing studies but they are not as strong and your decision about both classification and what kinds of data you would be comfortable with, if you decide to downclassify, you need to take that into account.

DR. THRUPP: I hope you are not coming from both sides of your mouth, now, Steve because I thought I heard you this morning say that we could make the recommendation that postmarketing surveillance be a strong recommendation to include picking up some of the potential problems.

at

DR. GUTMAN: That is different. I am talking about actually doing studies beyond--I was talking about you could require certain changes, come back in. You can certainly suggest that we do postmarket studies. I am hopeful that postmarket studies, in the context of 510(k)s will work, but since I believe in truth in advertising, I don't know how well they will work.

DR. THRUPP: And you are introducing a concept we haven't really discussed today at length, and I don't propose we get into it, but there is a difference between postmarketing studies as opposed to simple postmarketing surveillance.

We may want to address how we word it, the difference between studies and surveillance for postmarketing.

DR. GUTMAN: I actually have an additional insight I would like to share with you.

MS. SHIVELY: Roxanne Shively. I am a reviewer in the Microbiology Branch. I have looked at many of these submissions over the years, and also worked on the guidance document back then. One of the areas in the guidance document that hadn't been well developed at the time was reproducibility.

In the intervening years, we have tended to expand

at

that section to cover multiple-site testing with inoculum effects to really assess the ability of different labs to get the same results with known organisms.

Certainly, that may be one area, Dr. Charache, that would meet your concerns and also the other concerns with really challenging the system at the site where it is to be used with known resistant strains. I believe right now--help me; is it 20 strains--right now it is a fairly minimal number of ten strains at each of three sites. Those three sites can be different than the performance sites.

DR. THRUPP: Do we have other suggestions on question 2 on the review criteria that haven't been brought up yet?

DR. CHARACHE: This is a question, again, trying to get out from under some of the administrative hassles and delays associated with the--I am wondering, if we were to suggest a level II classification along with a rewrite of the guidelines so that there is a current active document to provide guidance, that whether we could add a request that certain factors be addressed and these are those which, in part, are coming up now and, in part, reflected the discussion this morning when we asked whether this was helpful to you or not, things like the design and manufacturer issues that you felt might be helpful.

at

DR. GUTMAN: My understanding, and Freddie or Heather could correct me if I am wrong, but my understanding is that, as you move forward, if you decide to make this a class II, you can put whatever recommendations you think appropriate.

DR. CHARACHE: Certainly, if we identify a need to make a change in a panel, whether it is methicillin resistance, we certainly don't want to wait an unnecessary three months to get it through. But if it did take longer than 90 days to insure that it was being done as you wish, can we address that?

DR. GUTMAN: Oh, yes. You are free to make any recommendations you want and we will do the best we can to deal with them.

DR. CHARACHE: Then I think my final question, and I am sorry for having so many questions--

DR. GUTMAN: No; that is what we pay the big bucks for.

DR. CHARACHE: If you want to pay me more, I will talk longer.

DR. GUTMAN: I deserve that.

DR. CHARACHE: That has to do with predicate devices. Is there any way or cautions that this group might add to indicate what we might think could be included as a

at

predicate device and some cautions of what we might think might not be considered a predicate device.

DR. GUTMAN: That is fair game, also.

DR. THRUPP: Do you have some suggestions along that score?

DR. CHARACHE: That last one?

DR. THRUPP: That last point. It is an important generic point but I wonder what you feel we could say at the moment.

DR. CHARACHE: I think I would say that, like the drawing up of the guidance document, I don't think I would want to do this very lightly off the top of my head. But I would love to hear anybody else's thoughts on this. I certainly wouldn't think the Crystal system for Becton Dickenson would count as a predicate in either direction.

So I think, if it is going to be your rapid test as opposed to an automated one, I think that should be defined. But it should probably be rapid and semi-automated or something that indicates that it covers a range of antibiotics and not a single analyte, or whatever we want to say.

DR. GUTMAN: We would actually appreciate your thoughts on how to establish the performance of this device. That would be of great interest to us.

at

DR. THRUPP: Any other comments on question 2?

Let's go on to question 3, some of which have already been brought up, but, "Are there other methods available to review data to permit assessment of the safety and effectiveness of the short-term incubation device as a class II?"

Obviously, we have been mentioning suggestions for expanded special controls, of several varieties. Is that the primary mechanism? Does anybody have any other suggestions for other methods? Dr. Edelstein?

DR. ZABRANSKY: Let's see your laundry list.

DR. EDELSTEIN: It will come one by one. I would like to suggest that the present surveillance system that the manufacturers currently use to detect problems with the susceptibility system be formalized by some mechanism; in other words, that there be a formal statement of how this should be undertaken.

I guess there needn't be any changes in terms of reporting since I guess reporting is required whenever a report is made. But currently it seems as if it is a passive mechanism that may differ from manufacturer to manufacturer. We know reasonably well that the system that the current manufacturers use seems to be a very good one, but we would want to be certain that other manufacturers

at

would hew the same line.

So I think it would be good--I don't know whether that would be called postmarketing surveillance or some other term.

DR. THRUPP: I think what was being described was generally postmarketing surveillance as opposed to FDA-suggested postmarketing further studies.

DR. EDELSTEIN: Yes.

DR. ZABRANSKY: The annual report that is submitted; this is required as a GMP, is it not?

DR. POOLE: The annual report is required as one of the conditions of approval for all class III devices.

DR. ZABRANSKY: But what about class II?

DR. POOLE: They don't require annual reports.

DR. ZABRANSKY: So we could require some type of annual report to include some of the information that Dr. Edelstein was mentioning.

DR. GATES: I guess I am unclear what Dr. Edelstein is saying in terms of additional information. There is in the quality system regulation, complaint handling and dealing with any customer issues that may come in from any source. Are you talking about more of an active, going out there and finding it sort of thing?

DR. EDELSTEIN: Yes; I am talking about an active

at

mechanism of, perhaps, actively polling users or a representative sample of users. I am not certain what mechanism would be most appropriate, but I think that something that is more active would be beneficial.

DR. GATES: Okay.

DR. ZABRANSKY: Part of the GMP process is that when the inspectors come in, they look for some of these types of reports or complaints and review these. But they only have to be held in hand. They don't have to be submitted to anybody unless specifically requested; isn't that correct?

DR. THRUPP: Unless the FDA, as a special condition, adds--

DR. ZABRANSKY: Because they are following up on a pharmacopeia complaint or something.

DR. THRUPP: A guide that these be included in some kind of an annual report even if it isn't the old PMA format.

DR. EDELSTEIN: Would also like to suggest that there, in fact, be an annual report but that it only include a literature review and summary of significant adverse effect reports. So it wouldn't, necessarily, include reprints and it could just indicate trends with sample references.

at

DR. THRUPP: You mean that the follow ups that you are suggesting would include literature review.

DR. EDELSTEIN: No, no. Currently, it is my understanding, the annual report requires reprints of all literature that the manufacturer has available regarding the performance of the device.

DR. GUTMAN: You are really testing us in terms of new ground. We feel very comfortable in telling you that we think we can write in the special control some kind of language that would allow us to call for new 510(k) when performance changed because of a biological shift in the organism or because of an unexpected change in performance.

We think we can build that into the special control. We are not quite as sure that we can somehow or other convert the special control into an annual report requirement. If you feel so uncomfortable about this downclassification that you are not willing to give up the annual report, then maybe you ought to consider voting against it.

DR. THRUPP: I think the concern was well put. I don't get the sense that the panel is uncomfortable with the procedures that the current two manufacturers, and we have heard the most detail from the one, are necessarily utilizing because they are making, obviously, a broad and

at

historically long time they have been at this.

Dr. Charache has pointed out that, despite this, there were some possible deficiencies in what might have been looked at. But I think the greater concern is precedent or predicate of what is going to happen in the future.

DR. GUTMAN: I think it might be possible, within the context of a special control, to look at broader issues. It certainly is novel for us, but I wouldn't suggest that we couldn't attempt to do that and the issue would be to look at the surveillance program and make sure that it is in place and it is reasonable and that it will identify shifts in resistance that would be of concern to us and should provoke a new submission.

I think we could try that, yes.

DR. THRUPP: I would hope that the current manufacturers who have a body of data and who have a system going would be reasonably happy to codify that and formalize it so that their product would continue to be a leader, so to speak, in the field and have it be well substantiated over the years.

DR. GATES: You do know that there is stipulation for medical device reporting, regardless of whatever the device or class is. Could it be subsumed under something

at

like that?

DR. EDELSTEIN: That is still a passive system. Currently, I think that the manufacturers do have actually a method of obtaining more than passive information via their user group meetings, for example, where that might qualify as active surveillance in which they would poll the users groups to determine if they have had significant programs.

DR. GATES: But I guess the issue is divided into two places. One is passive versus active surveillance of whatever it is and the other one is what the mechanism is for notifying the FDA of whatever that information is.

You can make the argument that, well, there should be active gathering of the information but then is an MDR report a substitute for the mechanism of getting that information. I don't know.

DR. EDELSTEIN: I don't know the answer to that. I am assuming that the reporting requirements won't change.

DR. GATES: You mean in case of death and serious injury, and, if it is not that--

DR. THRUPP: An active or somehow semiactive surveillance system might not all be negative. It might, indeed, be of very much value to the company as well as to the medical community if the problems had all been solved, or were being solved, and the data were excellent. I would

at

think that would be important to have routinely reported.

DR. GATES: I agree that it is in everybody's interest to keep track of what is happening in the field and emerging resistance and everything else, that everybody needs to keep track of that. I guess it is how that gets--

DR. GUTMAN: I can point out that both the companies and, for better or for worse, the agency do also have access to proficiency-testing surveys which is another sentinel. It may not be as lively as the user groups, but it is a way of getting information on performance.

DR. KADREE: I just wanted to add that retaining the annual report, actually, even though we were to change the classification to a class II, won't actually be detrimental because the industry will still have the advantage of having an expedited review as well as a level of intensity of review that is going to be dependent upon what kinds of changes are being asked.

So it is still, to me, a major advantage to change from a III to the II even if you do keep the annual report. I think there are enough concerns that have been expressed today to indicate that it might not be a bad idea to keep the annual reporting until we are more clear about some of the issues.

DR. THRUPP: Paul, you were next. You had a long

at

laundry list, you said. I think we haven't finished your laundry list.

DR. EDELSTEIN: The only thing I would like to say about the annual report is it is my understanding that presently it includes factors other than performance or trends in resistance. It includes such factors as manufacturing changes that I would be willing to let the manufacturer keep on file.

So that is why I am saying not to call this the same sort of annual report but just an abbreviated report that would have to do solely with performance.

DR. KADREE: I am not disagreeing with you. I am just saying that just keeping the annual report in isn't much of a hazard, really, because they still have tremendous benefits.

DR. CHARACHE: What I am hearing is everybody kind of aiming for a II.5. What I am wondering, and this, I guess, Dr. Gutman would have to help us with, is what is the best way to get to a II.5. Is it to put some controls on a II or is it to loosen things from a III.

DR. THRUPP: Mel is from New Jersey. He has got to be a politician.

DR. CHARACHE: So am I.

DR. GUTMAN: I just have to tell you,

at

speaking--and the reviewers always keep me honest, I want you to recognize that we don't, necessarily, anticipate every annual report with absolute glee and joy, put it on the top of our pile of things to read, consume every bit of information on it and assume that it is gospel.

So I don't know, within the construct of what we do--we certainly want to do what is right by this product line and put the right controls in place and are willing to consider anything you recommend to make this--it probably deserves to be a II.5, or maybe even something in that order.

There is a great deal of change here. Actually, it is probably impossible for me to give you square and straight answer since there is so much change as to which is the better route, to make it the II.5 by kicking the 510(k) up or by bringing the PMA down.

We will try and do the best we can with whatever decision is made, but I think you are unnecessarily obsessive over the annual report. I apologize for saying that.

DR. THRUPP: One rationalization, Steve, might be that the annual reports might stack up except if you read in the local ASM chapter or The New York Times or the Inquirer or something that there is another Andromeda Strain that

at

somebody is talking about, you would then have some information in your files that you could say, "Gee; did we look at this," and you might have some data whereas you are reacting without any information otherwise.

DR. GUTMAN: It is not without value. It does have value so I don't wish to suggest that either.

DR. GATES: I guess, as Dr. Gutman was saying, an annual report is an annual report and I think if we are going to keep track of all this stuff, the data ought to be coming in as it is made known.

From what I have gotten before, between the Internet and reviewers looking at everything and things in journals and stuff, there are plenty of conduits for getting emerging information to the FDA in a lot faster manner, basically.

DR. THRUPP: Mel, we didn't hear your resolution.

DR. WEINSTEIN: I guess it was sort of a corollary to the II.5 question II.5 question. That was, in your presentation earlier, Dr. Gutman, you alluded to some sort of an expedited or improved class III. I was trying to remember exactly what that would consist of as we were talking about whether to do this as a II or a II.5 or whatever.

DR. GUTMAN: The division has in place, and it

at

hasn't started yet, but it has begun to develop parameters for what we are calling a streamlined PMA. The streamlined PMA is one which all of the controls in place that you are talking about now, things like, certainly, not necessarily premarket GMP but assurance of GMP at some point in the process, we would require annual reports although we are talking about changing that, making them abbreviated, maybe making them every three years instead of every year, making them the first two years instead of forever.

We are looking at abbreviating the summary of safety and effectiveness which is an immense job for both the companies and for us, looking at doing real-time interactions, looking at chances in the delegation of signoff authority, a whole variety of things that is untested.

I can tell you that the tier III 510(k) panel track with a high level, the high-octane 510(k)s, work. I tell you that with assurance. It works well for us and the streamlined PMA is exciting. But it is not approved a product yet.

DR. THRUPP: Dr. Edelstein, did you have some other additions to your laundry list?

DR. EDELSTEIN: I had some additions to things I would like to see incorporated into the use conditions of

at

the devices. They are relatively view. One is I think that it would be helpful to the user to list the performance of the system by drug-bug combination rather than, I think, currently just by organism--or antibiotic, I guess, is what it is.

The other is that there be a requirement for use of either a nephelometer or a 3M device for preparing the inoculum. Currently, it is left up to the user to decide if they are going to use a turbidity standard whether they do it visually or use a nephelometer.

DR. KADREE: I would like to add to that list under performance that specific mention be made about the problems with vancomycin-resistant organisms and so forth so that users will realize that the reliability of the test in that area may be poor and so treatment should be based on the combination of the clinical picture and the susceptibility data and not just on the susceptibility data.

DR. THRUPP: Do we have any other suggestions for the laundry list? **Industry Response**

DR. THRUPP: If not, we have a segment allocated for any further responses from industry or from the audience. I did see a couple of hands that were waving during this discussion so now would be the appropriate time to get into the act.

at

Come to the microphone and identify yourself, please.

MR. LYNCH: I am Ron Lynch. I am from MicroScan. I wanted to go back and try to readdress the issue that it seems like the panel is really struggling with. It seems like the overriding issue here is that you are concerned about the accuracy of the test and what is driving that is the concern for emerging resistance.

As an industry, we are really aware of that issue and we are addressing it as best we can on a regular basis. Our counterparts at the FDA are very concerned also and every submission we have, we deal with what we know at that point in time is the resistance issue that we face. And we try to do sufficient testing.

If we do have issues, we have limitations in our product to handle that. The overriding issue, I think, is that it is a timing thing. When we release our product, the resistance is happening out there so fast that we can't keep up. So, consequently, we are behind the eight-ball and going to a 510(k) will help us because it will outreduce our response time to get to these problems.

I think there were a couple of good suggestions made about the challenge set, making sure we have an up-to-date challenge set. That will help us. But some of

at

the other things that we are talking about, the year-end report and some of those things, are really--I don't think they deliver a lot of value.

I think the big thing I heard that would deliver value is to make sure that we have the most accurate, up-to-date challenge set at the time from a resistance standpoint. Then, going to the 510(k) or class II will allow us to quickly address the problem in the field.

So that was my comment. I hope that helps the panel a little. Thank you.

MR. MULDER: Just a couple of things. I know that the guidance document was created to be an ongoing, changing document. It just, unfortunately, hasn't changed over the years. There has always seemed to be something more important come up in the division and they have had overwhelming issues to deal with. That is one of the reasons we would like to get in the class II.

Right now, the PMA process, the supplement process, is going quickly, but we know things come up and things change very rapidly. I think there do need to be some changes in the guidelines. The industry has gotten together as a whole and made recommendations of where we felt there should be changes to it.

As Sharon said, we are willing to do anything it

at

takes to help the FDA on that. I have a little concern with constantly updating the document in that we never know where we are at, then. Sometimes, there were issues in the past where we would go out and run the trials and we are kind of trying to hit a moving target. That really makes it difficult.

So you can make changes, but then you can't just keep making changes constantly because it is difficult on everybody. It is difficult on the reviewers, on everybody. So I would hope, if we are going to make changes in the document, that we can make some changes and not have it as a moving target as has happened in the past.

There is a lot of information now available to companies as far as the susceptibility trends. Clyde Thornberry's TSN network now, where it is on-line information as far as resistant, resistant trends, you can get basically all the information you need from last week to two weeks ago across the United States as far as the different resistant patterns and what the trends are out there.

So it is available to industry. We are looking at it. We do use it. We use that when we develop our test as far as looking at the trends of what we see in the field. I do agree the CDC panel needs to be updated and new organisms

at

put in there, but then you always run into the problem of updating that panel, who is in charge of updating, how often do you update.

That sometimes becomes another problem as far as trying to coordinate that all the time of having somebody maintain that set, maybe some manufacturer has one set, different manufacturer has another set and then you send them out to different people.

So a lot of change are good, but sometimes they create whole other issues when we make a lot of those changes to the documents.

I agree on the annual report, there is a lot of information in the annual report that would not relate to the performance issue. It usually is after the fact, sometimes way after the fact. I think most of the reviewers see the literature and basically see what we submit them, anyhow. Very rarely is there a surprise that they find in the annual report.

As far as the NCCLS standards pertaining to automated systems, I don't know that that will ever be a mention of automated systems and standards. They are set up for the standard method, not for automated or other systems. I can see using them as standards, but I don't know that there will ever be any mention in those standards related to

at

automated systems.

DR. THRUPP: That may be more precise, I think, for short incubation rather than necessarily automated. Well, they are both.

MR. MULDER: But the NCCLS are for a standard methodology, not to relate to any other methodology. The issue of the no-reports--in our petition, we had no reports that caused or contributed to illness or death. There were no MDRs filed on any of our products, not that we haven't gotten issues in from the field.

That is how we find out that there are problems with detection. That wasn't the statement that we were trying to make in there, that we never get any complaints from the field.

Unless somebody has some other questions for me--the one issue I see is taking a long time to make changes in the guidance document, if we agree it needs changes. I would hate to see changes in the guidance document drag out for three or four or five years before they finally happen. That kind of puts us and the FDA in limbo, too, as far as how do we review something that is now coming in--we know we are going to change the guidance document.

It doesn't meet what we are changing to so they

at

are going to have to review it to what they have. So I would hope that things could change in a hurry if they are going to change because it puts them in a bad situation, everybody in a bad situation.

DR. GUTMAN: It is my understanding that you can't put a downclassification through until you have a special control, so there is a certain time constraint in terms of moving that forward. The special control would have to be finalized before the classification was finalized, or the classification change.

MR. MULDER: We had planned to submit the same amount of data that we currently do as a PMA. That was our original intent as to not change to the actual 510(k) but stay with the same amount of data that was required currently.

DR. GUTMAN: At the heart of the angst here is this issue. It is an appropriate issue because it is one that many of my colleagues share. It is what happens when there are changes that are observed. We have had in the recent past an instance of where we noticed a problem with strep resistance to penicillin.

It did occur through medical device reporting, failure reporting, and it did create changes that may have delighted, annoyed or been something in between for the

at

manufacturing community. We certainly took it seriously from the standpoint of the user community and would view it as not a fantastic success.

I think it was a success and the branch deserves some credit for expediting a lot of changes very quickly. But we did notice that it was a problem. It is a problem that probably needs to be fixed better in terms of responsiveness to those kinds of issues and it is a problem that I don't think would be fixed by annual reports and didn't seem to play out across PMAs and 510(k)s.

It is a problem we probably need to fix some other way, whether there is some way as a special control or whether we need to reengineer the MDR system, itself, or reengineer our responses to the MDRs or we have to figure out other ways of interacting with professionals.

This is not a trivial or unimportant problem. It is just that there is some ambivalence in my own mind as to whether this is a problem that actually is fixed by the classification system or it is a problem where you need to look for fixes in other ways.

DR. THRUPP: You raise a very good example. This is the kind of example that, perhaps, we were looking for in terms of how, administratively, things might happen and whether they would be changed or not.

at

DR. GUTMAN: It was an equal-opportunity problem for PMAs and 510(k)s and I don't think we saw a change in them.

DR. THRUPP: Was this in Strep viridans or pneumococci? Strep pneumo. Hopefully, theoretically, at least, the suggestions for a systematic postmarketing system of some kind rather than just ad lib might have had a better chance to give you a chance to be at least one jump ahead of--

DR. GUTMAN: There is a theoretical construct that should play here. I just don't know if I can, with an honest face, tell you it will play. But the new design controls that apply to this include the need to survey input and output and to make adjustments based on information that comes in in the marketing system.

So there are quality system regs in place that, if they work the way they are spirited and targeted to work, would make this less of an issue in the future. I hope that is the case. I won't promise it is the case. It is supposed to be the case.

DR. THRUPP: But the bottom line of that issue for today's deliberation is will it be helpful to all concerned and especially the patient's and the public's health if we do include in our special conditions some--

at

DR. GUTMAN: It can't be harmful. The issue is how well we can, within our changing environment, implement your suggestion.

DR. THRUPP: Whether you are going to have enough help to be able to respond.

MS. CULLEN: I just wanted to respond to the questions and concerns about how do we--and I do mean the collective "we--" how do we monitor performance after a product is released and how do we continually evaluate the ability of our systems to detect resistance.

As you have rightfully pointed out, the emerging resistance doesn't come from the manufacturer. They are first noted in the institutions. Those do get reported to us, previously in the GMPs and currently in the new quality system regulations. We are required to investigate complaints.

When we get these strains in, if there is a discrepancy, we need to adequately investigate those. If part of that investigation is that our product no longer meets performance claims, then we need to follow through on that. That doesn't change.

I think there was also a point made of annual reports or once a year. The timeliness of the Strep pneumo and the enterococci wouldn't have--it could have been

at

another eleven months to have acted on that situation.

It was an equal-opportunity situation of both overnight systems and rapid systems. So I think we have a lot of controls with our current processing systems that allow us to monitor performance, act on it and make improvements. The downclassification will help us be more flexible and timely in doing that.

I don't know that an annual report, like I said, a year later will help that. I think some provisions--it is within our responsibility to follow up on these. So that could be clarified.

I also did want to make one other point on the number of strains in sites. For the sake of testing more to get more data, I would just caution us to make sure that we are not collecting data just to make ourselves feel better, that it is with value, and things like looking at reproducibility strains amongst various sites which we currently do, and if we need to take into consideration inoculum, if that is a parameter, and does it affect our system.

It may affect different systems in different ways. That would and should be taken into consideration but I don't know that lots of sites and lots of susceptible strains are really going to tell us what we need to know

at

about detecting resistance.

DR. THRUPP: What you are doing sounds great. So does Mr. Mulder's. The question is would it be for someone else who comes along with a so-called predicate, now, as far as precedence, wouldn't be helpful for the FDA to have a suggestion, as a special control, that there be a formalized system of some reasonable format for doing just what you say you are doing, so it is standardized, so you are doing the same thing and there is a level playing field.

MS. CULLEN: Personal opinion. I think, and I can't remember the exact language--you used some language earlier in the day about if there are performance issues that are reported and, as part of our investigations, we find having a requirement that those be addressed either through labeling limitations or modifications to our systems to improve them and address them.

DR. GUTMAN: No; actually, I was suggesting something stronger which is that, as part of the special control, when things go out of control to a certain extent, I was actually suggesting a new 510(k) be submitted. Now, that may be stronger than you like or stronger than panel likes.

But that was actually what I put on the table was the notion that you write in, this is part of the special

at

control, a notion that when you see enough performance drift--I don't know what "enough" is--but when you see performance drift that, rather than wait for an MDR or wait for the FDA to become interactive with the companies or to become interactive with other government agencies like CDC, that the companies have a moral and legal and special-control obligation to immediately kick in and correct it.

In light of what we just said about the equal-opportunity employment here and the fact that it affects both rapid systems and not-so-rapid systems, the panel might choose to recommend they be used for all systems, although I am not supposed to lead you.

DR. THRUPP: Any other comments?

MR. SANDERS: I am Steve Sanders. I am with bioMerieux Vitek. Just to reinforce what Steve Gutman just indicated, and to clarify. The controls that we have, the collection analysis, evaluation and review of information from the field is part of the general quality-system regulation that applies to all devices, whether they are class I, II or III or even exempt devices.

The quality systems regulation requires that all complaints be evaluated and those that affect performance be investigated. There is another section that requires

at

corrective and preventive action where you take all quality data, internal, external and anything that you hear, analyze that on a periodic basis and, from that, take action to improve your overall quality system so that there are a number of controls that are built in to the quality system regulation of the type that you are concerned with here.

The other thing that I would like to point out is with the types of systems we are talking about, manufacturers typically have hot lines that take in calls from customers to address any one of a big variety of issues from how do I do this to something that is directly, already in the instructions and just pointing to where the right direction is to performance issues.

There are a large number of those and there is an ongoing system that we have. We get a lot of data. I would also like to point out that there are, such as the surveillance network and other publications, a lot of information already available to the agency and to manufacturers regarding emerging resistance, and more coming on line.

This is an opportunity area that not only the surveillance network but, I believe, that there are other competitive networks that are being generated on the Internet so that you, as users, have the ability to see what

at

is going on in the resistance area outside.

Finally, should an issue arise, I believe that there is no real difference in the controls, that FDA can, at any time, issue a safety alert or ask manufacturers to do things to make corrections to products. That is also independent of classification.

So, as you consider this, I would like you to understand that there is a lot of stuff that is already there in class II as well as others of the type of thing which we have been talking about today.

Thank you.

DR. THRUPP: Any other comments?

DR. CHARACHE: Just one point. I have been thinking about the comment that Ross made. I wondered--I think what I was trying to address in the petition is the fact that one reason for classifying a device as a class III is because it is clinically important and that there is a risk if it doesn't work properly.

It was in that setting that I was reading the statement about the reliance on reports by physicians that there were problems. So, as you read this item 2, it reads, "During the history of STIC use, there have been few reports of adverse experiences associated with the use of the devices. Considering the number of tests performed,

at

retaining the class III designation is not supported by any substantiated reasons relating to the increased potential for risk or harm to patients."

What I am saying is that is an irrelevancy, that the doctors don't know when there is risk or harm with the device is used. Very frequently, the laboratorian doesn't either. I am thinking it took us three years with Christine Sanders' assistance to get NCCLS to come up with a way of addressing to VRE and similarly the ESBL.

So, I was concerned about that, therefore, being as a precedent for why it is not an important test. I think it is an important test and that has to be retained.

I think, also, we have to be careful because not all industry concerns, although they have the right goals, respond in the same way to challenges. Some seem to have a little more difficulty seeing the problem than others may have.

DR. THRUPP: Any other comments?

#### **Panel Vote and Recommendations**

DR. THRUPP: We are moving on to the classification questionnaire which the panel members have a copy of. We are going to go around the table for a yea/nay vote on these and some summary suggestions.

Before we do that, Freddie Poole has an

at

administrative clarification.

DR. POOLE: Only voting members participate in the actual vote of whether or not we reclassify or remain as a class III. The voting members are Lauri Thrupp, Chairperson. He only votes to break the tie. Patricia Charache. Margaret Kadree. Steven Specter. Appointed to temporary voting status to fill the quorum, we have a letter from Dr. Burlington.

"Pursuant to the authority granted under the Medical Device Advisory Committee charter dated October 27, 1990, as amended April 20, 1995, I hereby appoint the following people as voting members of the Microbiology Devices Panel for the meeting on February 13, 1998: Paul Edelstein, M.D., Ron Zabransky, Ph.D.

"For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting."

It is signed D. Bruce Burlington, M.D., Director for the Center for Devices and Radiological Health.

The voting is done in a sort of different manner. We have an in vitro diagnostic product classification questionnaire and we will go through items 1 through 7.

at

Each member, beside marking the questionnaire, will give a response to Dr. Thrupp as he goes around and asks.

DR. THRUPP: Does everybody have a copy of the questionnaire?

DR. WEINSTEIN: Can non-voting members see this questionnaire?

DR. THRUPP: Everybody around the table is a voting member; right? Consumer and industry are not.

DR. POOLE: And the other consultants to the panel are not.

DR. THRUPP: Can we get an unrecorded vote from them?

DR. POOLE: Yes.

DR. THRUPP: Question No. 1; is the in vitro diagnostic product or information derived from its use potentially hazardous to life, health or well-being when put to its intended use? This is a yes or no.

DR. EDELSTEIN: Yes.

DR. THRUPP: For the non-voting record. Dr. Ng?

DR. NG: Yes.

DR. WEINSTEIN: Yes.

DR. ZABRANSKY: Yes.

DR. KADREE: Yes.

DR. SPECTER: Yes.

at

DR. CHARACHE: Yes.

DR. THRUPP: Unanimous. I don't need to break that tie.

Is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device? I am assuming when we say "general controls," as opposed to the special controls.

DR. CHARACHE: The petition's checks on are page 7.

DR. EDELSTEIN: No.

DR. NG: No.

DR. WEINSTEIN: No.

DR. ZABRANSKY: No.

DR. KADREE: No.

DR. SPECTER: No.

DR. CHARACHE: No.

DR. THRUPP: Next question; considering the nature and complexity of the product and the available scientific and medical information, is there sufficient information to establish a special control or set of special controls in order to provide reasonable assurance of the safety and effectiveness of the device?

The responses here are stratified according to

at

class III or class II. Freddie, may you should--if we answer--

DR. POOLE: If you answer yes, that means you could classify it into class II. If you answer no, then that means it should be classified in class III.

DR. THRUPP: This doesn't say that the special controls are already in effect. It says that there is sufficient information that one could recommend--

DR. EDELSTEIN: You answer that in part 3b.

DR. THRUPP: Right.

DR. EDELSTEIN: Yes.

DR. NG: Yes.

DR. WEINSTEIN: Yes.

DR. ZABRANSKY: Yes.

DR. KADREE: Yes.

DR. SPECTER: Yes.

DR. CHARACHE: Yes.

DR. THRUPP: We are making progress. We are in class II.

DR. ZABRANSKY: Now comes the real part.

DR. THRUPP: Now comes the morning again, 3b. Check the special controls needed to provide such reasonable assurances. Since there has been a unanimous yes to 3a, we have got some work for 3b. Perhaps, we could ask for which

at

of these choices you would check in your response. Do we want to get the miscellaneous others at the same time?

DR. POOLE: Yes, if you could just give "others" and which they are.

DR. EDELSTEIN: Before I do that, I need some guidance on how to fill out the form. There is a check box that says yes/no. Does that mean that it pertains to the items on the left-hand column, or, if you want something in the left-hand column, you tick the box? I don't understand the yes and no in the intermediate column.

DR. POOLE: It means that you only do this if you answered yes in 3a.

DR. EDELSTEIN: I know. But there is the yes/no in the intermediate column.

DR. POOLE: Yes. It is redundant. It is a reminder of the way you answered in item 3a.

DR. EDELSTEIN: Okay.

DR. SPECTER: If you have nothing to add, you put no. If you have things to check off, you are going to put yes.

DR. ZABRANSKY: And then check them off accordingly.

DR. EDELSTEIN: Okay; I got it. You can do my taxes this year. So, my answers to 3b are; yes, I think

at

there should be postmarket surveillance. Yes, I think there should be performance standards. Yes, I think there should be testing guidelines. I do not believe there needs to be device tracking. For other requirements, I think that those might be covered under testing guidelines already in terms of what I had suggested--suggested changes for the user.

DR. THRUPP: You would imply, for example, that things like a revised challenge set or a supplemental challenge set would come either under performance guidelines or testing guidelines or both.

DR. EDELSTEIN: That's correct. That is my understanding of this form.

DR. CHARACHE: Would we put definition of the predicate device under "other?"

DR. POOLE: No.

DR. CHARACHE: That would be later on.

DR. KADREE: Performance standard; no?

DR. ZABRANSKY: Where would you put the updating of the review criteria? I would put that under "other."

DR. POOLE: Under "other."

DR. KADREE: May I make a suggestion to make this a little bit easier. Why don't we determine, up front, what things we are going to put in the category of "other," and then go around the room and ask people to vote on each of

at

the specific items? So, postmarket surveillance, go around the room. Then performance standards, and so forth, so we can get a feel for how the voting is going.

Otherwise, I think it is difficult to ascertain which of these criteria the majority of the group think would recommend to be put in place.

DR. THRUPP: That is a good point. I was thinking we could do it cross-sectional instead of longitudinal.

DR. CHARACHE: You could just ask how many people want his pattern which was three yeses and one no.

DR. THRUPP: He didn't finish his "others." We have concluded that at least some of the things that were discussed could go under testing guidelines and performance standards.

DR. EDELSTEIN: It is still unclear to me whether revision of the '91 guidance document is included under performance standards or whether that is included as "other."

DR. KADREE: The performance standards are different from the review criteria guidance document.

DR. EDELSTEIN: Then I would include, as the only other addition, the guidance document be updated.

DR. THRUPP: Perhaps that is part of 4a.

DR. EDELSTEIN: Ah.

at

DR. THRUPP: So maybe we don't have to put that under 3b.

DR. EDELSTEIN: No, no. That is a performance standard.

DR. THRUPP: Okay. So we want to put under "other," update of the performance guidelines. Let's see. What else do you want to throw in there while we have you on the firing line?

DR. EDELSTEIN: The other things I am a little unclear of; for example, the use of a new challenge panel, the updating of a challenge panel. I would interpret that to mean that those would be changes that I would want in the guidance document.

DR. THRUPP: That is part of updating the document. I think for the purposes of this petition, I would interpret those as being covered. The challenge sets and upgrading them would be covered under either performance or testing guidelines, I am not sure which.

DR. EDELSTEIN: I don't know if it would make it easier, but maybe I should just restate what I would like changed and then wherever that goes, people can decide on the form. Actually, after hearing the comments regarding the annual review, I withdraw my recommendation that there be an annual review submitted.

at

I would like to see, in the use of the test, a specification that either a nephelometer or a 3M device be used for preparing the inoculum density and that, specifically, visual comparison with barium sulfate standard be omitted from the document or, in fact, discouraged by the product insert.

I would like to see, in the guidance document, a requirement for the use of an updated challenge panel both for us internally by the company as well as externally by the test sites. I would like to see a change in how the acceptable error rates are expressed so that those are expressed as a range rather than as a mean number.

I would like to see that there be some form of postmarket surveillance that was in an active format. I would like to make a statement that the predicate device for future applications be conventional susceptibility testing methods and not rapid testing methods.

DR. ZABRANSKY: Excuse me; say that again.

DR. EDELSTEIN: That the predicate device for new applications be a conventional testing method--in other words, greater than 16 hours--as opposed to a less-than-16-hour reference standard. Finally, based on Dr. Gutman's comments, I would like to see a statement saying that if the agency thought that preclearance inspection of

at

the manufacturer was necessary that this be optional, that it be made clear that this is an option.

DR. GUTMAN: Can I just clarify something, that the predicate is irrelevant to us. What is very important to us is the standard against which you are comparing--

DR. EDELSTEIN: So I misstated it. Rather than saying predicate, I meant the reference standard. I'm sorry. That's it.

DR. POOLE: Before we go any further, we didn't do No. 1 to spell out the generic type of device that we want to see reclassified from class III to class II.

DR. EDELSTEIN: What do you suggest we put in there?

DR. POOLE: Because I think Dr. Zabransky had a question earlier about whether we should call them fully automated--

DR. ZABRANSKY: I would just remove the word "fully," to make it easy. Just make it "automated." That could imply fully automated or even semi-automated if that is acceptable to the panel, instead of going into too many words.

But we do have to retain the word "short-term incubation cycle," or some form of less than 16 hours.

DR. EDELSTEIN: Why don't we call it "rapid."

at

DR. ZABRANSKY: That's okay with me, too.

DR. CHARACHE: Unless you specify the time interval, "rapid" can be in the eye of the beholder.

DR. EDELSTEIN: I was going to say "rapid, less than 16 hours."

DR. CHARACHE: Yes.

DR. THRUPP: Why change--the term "short term--"

DR. SPECTER: Is also in the eye of the beholder.

DR. THRUPP: But the term STIC has been in the document literature. It has been around for some time. Why bother to change it? That part isn't really broken.

DR. SPECTER: No; that is not broken.

DR. THRUPP: But the "automated" is ambiguous.

DR. EDELSTEIN: So we need to know what to put in the blank. "Short-term incubation device for antimicrobial susceptibility--"

DR. ZABRANSKY: ASTIC.

DR. KADREE: STIC ASD.

DR. CHARACHE: But we better put antibiotic susceptibility testing in there somewhere.

DR. THRUPP: Device.

DR. SPECTER: The petition is for a STIC ASD whether you want to call it fully automated or not.

DR. THRUPP: The proposal on the floor is that we

at

term it "automated short-term incubation cycle antimicrobial susceptibility testing device." All in favor of that?

[Show of hands.]

DR. THRUPP: I think that was unanimous.

DR. WEINSTEIN: Even among those who can't vote.

DR. THRUPP: We heard a little rumor that we are not talking about antivirals or antifungals. So we should have antibacterial susceptibility testing device rather than just antimicrobial.

DR. POOLE: It can remain as antimicrobial susceptibility systems and in No. 2, indications for use, that is where you would indicate that it would be indicated only for use with bacteria and describe which bacteria.

DR. ZABRANSKY: Maybe the FDA doesn't care what the publishers of the journals and ASM have to say, but for the JCM and for AAC, antimicrobial refers strictly to bacterial and they specifically say antifungal or antiviral for the others.

DR. GUTMAN: No; we care. So you can semantically clarify that.

DR. POOLE: Thank you.

DR. THRUPP: I'm sorry, Dr. Gutman. What did you say?

DR. GUTMAN: If that is common use, we don't want

at

you to make up things that are not consistent with common use.

DR. THRUPP: So antimicrobial is okay.

DR. EDELSTEIN: I have already made enough cross-outs on my form.

MR. SANDERS: From the industry side--

DR. THRUPP: We are not supposed to have any more questions from industry but I can recognize one.

MR. SANDERS: In the definition of terms, here, I think we, in the industry, would kind of wonder, then, what do you define as automated versus others and is there really a need for a differentiation there? Is the issue really one of is it a short-term incubation rather than whether it is manual or automated.

DR. ZABRANSKY: We want to make sure we don't include things like Crystal.

DR. THRUPP: The data that has been discussed in most, if not all of the papers, have been relative to what is, I believe, semiautomated systems. That term has been carried forward. So, for us to get back into the debate of whether to remove "automated," I think, is not productive. If it is okay with the panel, why don't we just leave the modified term "automated."

MR. SANDERS: It doesn't bother us any.

at

DR. THRUPP: We have Dr. Edelstein's list of "others." Dr. Kadree's point is well taken, but let's see, in the interest of time, if we can get a vertical column agreement while we are going around.

Dr. Edelstein's marks for yes, on the postmarket surveillance; yes, on performance standards; yes, on testing guidelines; zero, don't bother with device tracking. And he mentioned items to be mentioned, to be spiffed up, updated, in the FDA performance guidelines.

Dr. Zabransky, postmarket surveillance?

DR. ZABRANSKY: Yes.

DR. THRUPP: Performance standards?

DR. ZABRANSKY: Yes.

DR. THRUPP: Testing guidelines?

DR. ZABRANSKY: Yes.

DR. THRUPP: Device tracking?

DR. ZABRANSKY: No.

DR. THRUPP: Do you ditto the updates in the guidelines or do you have some others or some deletions?

DR. ZABRANSKY: No, but I have listed just about all of them that were mentioned; review criteria, updated challenge organisms, panels. I make sure it says "panels," with an "s." The nephelometer. Error rates. Active postmarket surveillance/report. I think there still has to

at

be, maybe not an annual report and we are not talking about the annual--but maybe a summary approach that this information is constantly being looked at and, also, somehow that it sent to the FDA or seen by somebody that is going to act on it.

DR. THRUPP: Are you suggesting we separate out the annual summaries of some kind as opposed to Dr. Edelstein's suggestion that there merely be the process--

DR. ZABRANSKY: There has to be an active plan in place by the company that they are looking for this information. We have heard it verbally, that they are doing it.

DR. THRUPP: How about if the wording would suggest that the plan would include, as per good practice standards, that the FDA be notified as data would come in.

DR. ZABRANSKY: Yes; because this is affecting their performance claims, as has been mentioned.

DR. THRUPP: Without making it a formal annual report.

DR. ZABRANSKY: No. I don't want it to be formal annual. And then the issue about the reference method, one of the standard dilution methods, promulgated by NCCLS.

DR. ZABRANSKY: As a comment, although we are not voting on it yet, is that item No. 5 refers to "performance

at

standards above" so we have to be very careful about what we are going to check there of performance standards.

DR. POOLE: Could a representative from the sponsor of the petition come up and just explain to us your generic type, or describe the generic type of device, that you had asked to be reclassified so we could get a clear understanding of what we are voting for, the type of device? We have to be sure that this is what you have in mind.

If you want it narrowed for the--I hate to put words in your mouth--or if there were any variations to incubation.

MR. MULDER: The generic type of device that we submitted was automated. We will take out the "fully" and say "automated short-term incubation cycle antimicrobial susceptibility devices intended to determine the antimicrobial susceptibility of bacterial pathogens."

DR. ZABRANSKY: Fine.

DR. POOLE: Thanks.

DR. CHARACHE: Sounds perfect.

DR. THRUPP: Let's move on. Dr. Kadree?

DR. KADREE: Postmarket surveillance, performance standards and testing guidelines, yes. Device tracking, no. Under "other," review criteria guidance update. Nephelometer should be used for testing. Reference standard

at

for new applications should be the current gold standard, which is greater than 16 hours. Updated challenge panels. Active polling of labs by industry with regards to performance standards and testing. And notification of FDA with regards to new information that affect performance standards and testing guidelines.

DR. THRUPP: Thank you. Dr. Specter?

DR. SPECTER: I had postmarket surveillance, performance standards and testing guidelines and did not have device tracking. I only had two things, really, listed under "other." One pertained to the nephelometry, and I would word it somewhat differently only not to be limiting if other techniques we are not sure of just yet are as effective.

I would say something along the lines that something more rigorous than visual comparison of inoculum be used with an eg. of nephelometry leaving it open to other things. Then, the updating of panels, I think, is very important.

DR. CHARACHE: I have the same profile. I added premarketing manufacturing practices and design be permitted as considered appropriate.

DR. ZABRANSKY: Premarket?

DR. CHARACHE: Premarket, if they want to--

at

DR. THRUPP: Optional. I also included the updating of test panels, the other things that others have listed.

DR. THRUPP: Question 4a; is a regulatory performance standard--

DR. ZABRANSKY: You don't have to answer this one.

DR. THRUPP: We have already said yes to this.

DR. EDELSTEIN: I have to say I think that there was some disagreement amongst us regarding some of these added indications, specifically the requirement for annual report. I heard Dr. Kadree specify that she would like that unless I misunderstood.

DR. THRUPP: I don't think she said "annual." She said reporting in some way, which is what Dr. Zabransky said, too. You didn't want annual, either.

DR. EDELSTEIN: No; I didn't.

DR. THRUPP: So some communication mechanism be encouraged in some way. I think there is agreement on that. And we have already said we want a regulatory performance standard. I think that is all yes.

DR. CHARACHE: High priority?

DR. THRUPP: Does everybody want an adjective of "high priority" inserted into our recommendations there?

DR. ZABRANSKY: Do we answer 4a and 4b? This

at

applies to class III.

DR. THRUPP: No; it is II or III.

DR. ZABRANSKY: Oh; II or III. All right.

DR. POOLE: One clarification. Performance standards becomes mandatory and they are not the voluntary standards from other organizations such as NCCLS.

DR. EDELSTEIN: So we still need to answer the question regarding priority; is that correct?

DR. THRUPP: 4b refers to 4a. Does everybody vote for high priority.

[Affirmative responses.]

DR. THRUPP: We don't have any exceptions.

DR. KADREE: No exceptions.

DR. THRUPP: High priority.

For a device recommended for reclassification into class II, should the recommended regulatory performance standard be in place before the reclassification takes effect?

DR. CHARACHE: I think we would have to say yes, otherwise it will ten years before it is in place. If it is required, it will be done promptly.

DR. THRUPP: I am not sure that that is the tone, from the discussions of today. I am not sure it is fair for us to put the FDA under that kind of a box when we are

at

trying to make everything more efficient for everybody.

Dr. Gutman has already said that they are doing this. But we have got the issue before us on should we hold up this reclassification until a document which is going to have to be broadly commented on and is going to require some time.

DR. GUTMAN: Let me clarify this. I missed the last point but I will jump in, that we will have to develop a special guidance before the classification can go into effect. They go hand in hand. Our preference, if you decide to move into the class II arena, would be to allow us to default to voluntary guidance and then, when there is failure to comply with voluntary guidance, to attempt to--or bounce it back up to III, rather than to go with a mandatory standard because a mandatory standard will not occur in my lifetime.

It is a very long process. It would mean that we would need another hearing. If you really want to push us into that direction, that is not a practical thing. A more practical option would be to say to default to NCCLS' voluntary standards and to give us the encouragement that, when a company fails to meet those voluntary standards, we not find the product substantially equivalent in the 510(k) process. That would be a better choice for us.

at

DR. THRUPP: You threw in NCCLS standards as a voluntary standard. Is that what you meant to say? We have already brought up the issue that the NCCLS does not, necessarily, direct its guidelines to rapid methods nor to the aspect that automation may or may not entail. So I am not sure that NCCLS is an option.

DR. GUTMAN: We compare to the reference method and we might be able to go out and solicit some opinion about, for example, confidence intervals that Dr. Edelstein has put up as reasonable. And that would be a more facile way of dealing with this and, frankly, would benefit not only this product line but probably the product line that is more generally not rapid would be to try and establish some kind of performance parameters, in general.

That, from our perspective--it is not a better way but it is a more practical way to go.

DR. THRUPP: I think you picked the wrong example when you indicated the range of performance compliance and error rates because that is going to be a moving target in NCCLS, too. And that is a very difficult one.

As a way to move this on, I liked your initial phrase that if we could put in something recommending--what did you call it, "voluntary compliance with the spirit or the intent of the--" how should we word that in order to not

at

create a box for you and yet to allow things to move forward?

DR. CHARACHE: I don't think it is a good idea to refer to NCCLS standards when there are none that apply to this kind of device. You can still have a voluntary standard with a rewritten FDA standard.

DR. GUTMAN: Yes; that is what we would like.

DR. CHARACHE: So I would not refer to the NCCLS other than that it has information in it that can assist the manufacturer. But it is not a voluntary standard for this usage. There is none. So I think it would be very reasonable to have a voluntary standard that the FDA could use as they review the various 510(k)s that would come in under this.

So I would rather propose that there be a voluntary standard which will be an updated and rewritten FDA document. I think we are assuming that that document will be written with input from those who can best advise on this, certainly including industry.

DR. THRUPP: Can the standard be called the guidance document or is that not the same thing?

DR. CHARACHE: Yes; it could be called a guidance document.

DR. THRUPP: I am asking Steve.

at

DR. GUTMAN: The guidance document and the standard are, actually, spiritually a little different. The standard is more binding and the guidance document tends to allow for more flexibility.

DR. THRUPP: Again, if it was a standard written by you, or essentially for you, you wouldn't call it a voluntary standard.

DR. GUTMAN: We would call it a guidance and we would use it as a special control. I don't think we would use the terminology "standard." For us, in our language, at least, standard is a really big deal. It is almost like getting a new reg or--

DR. THRUPP: That is why none have been written, as you said, in your lifetime or in mine either.

DR. GUTMAN: And I am only 30.

DR. THRUPP: Would it be appropriate for the panel to vote yes then, but with a caveat that this be a voluntary updated guidance document? Is that a fair wording? Would the word "voluntary--"

DR. POOLE: I don't think so.

DR. ZABRANSKY: I don't think so. I don't think it would be voluntary if it was strictly FDA.

DR. EDELSTEIN: We are talking about 4a, still, aren't we?

at

DR. ZABRANSKY: In some ways, we are.

DR. POOLE: If you want something voluntary and not--a performance standard is always mandatory. So that means we have to go back to 3b and reconsider--if you really want performance standards, they are mandatory. If you want "other," such as the FDA review criteria document or guidance document, that would go under "other," and you would skip No. 4. In the guidance document, we could also recognize other voluntary standards.

DR. GATES: I just wanted to make sure I understood. What the issue is, they want to make sure whatever these are, guidelines, are promulgated that everybody is going to really follow them. They won't have a choice of yes, I will or I won't.

I think, regardless of the semantics, and I think it is basically a testing guideline, there are methods that the FDA has to make sure those guidelines are strictly followed, even if they are called voluntary standards or guidelines or whatever.

DR. KADREE: Once standards are written, they are not changed anymore, the way I understand.

DR. GATES: It speaks to the point that when everybody is trying to keep up with a rapidly emerging resistance and stuff, the last thing you want is a mandatory

at

standard to do that.

DR. EDELSTEIN: It sounds like what we need to do is revote in 3b specifically in regard to performance standards.

DR. CHARACHE: As it states in 3b, it says special controls. We do want special controls to address these. That is not saying--so that is okay.

DR. EDELSTEIN: That performance standards are a type of special control.

DR. GUTMAN: Guidance could be a special control.

DR. CHARACHE: So we just have to get rid of the second box which is performance standards.

DR. THRUPP: Could we, alternatively, to get the intent of what we want done, instead of word "standard," could we say "performance guides?"

DR. KADREE: Yes; and spell it out under "other." You would describe that as "other."

DR. CHARACHE: So it would be performance guidelines; right?

DR. POOLE: Yes.

DR. KADREE: Guidance. Guidelines means something different.

DR. GUTMAN: It could be guidance including performance guidelines, perhaps. Guidance with performance

at

guidelines. I think the operative word here is guidance.

DR. CHARACHE: Guidance with performance guidelines.

DR. KADREE: With performance guidelines.

DR. THRUPP: Sounds redundant to me.

DR. CHARACHE: We have got to get rid of box No. 2, and everything else is all right.

DR. POOLE: And skip over 4a and 4b.

DR. THRUPP: If I can summarize, do we need to vote again that we are removing performance standard or we are voting zero on performance standard.

DR. EDELSTEIN: That's correct.

DR. ZABRANSKY: Agreed.

DR. THRUPP: And we are adding, under "other," performance guidance--

DR. KADREE: No; guidance with performance guidelines.

DR. THRUPP: Guidance with performance guidelines.

DR. EDELSTEIN: Can we just have one master document that clarifies this, or the record, I am saying?

DR. POOLE: That is why you each have to fill out one. I'm sorry.

DR. EDELSTEIN: All right. Tell me, again, what the exact wording is, please.

at

DR. THRUPP: Instead of performance standard, we are voting no on that. We are asking, under "other," that a distinct, separate item be, "guidance with performance guidelines."

In order to be consistent, should we also, then, back to No. 5, should we also, instead of the term "performance standards," say guidance--

DR. KADREE: No; then the answer would be no.

DR. EDELSTEIN: No; it is not applicable.

DR. THRUPP: Okay; so the standard would stay there and we are not asking for the concrete document yet.

DR. CHARACHE: Not applicable. That's good.

DR. THRUPP: No. 6 is--

DR. KADREE: We have to make sure that everyone has the "not applicable" for 4a, 4b and 5, whether everyone votes that way. You don't have to vote that way.

DR. THRUPP: That is because of the word "standard" that is in those questions all the way through.

DR. KADREE: Right. And 6 is not applicable because it is not class III.

DR. THRUPP: We are now on the back of the page, 7a; can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use because of any potentiality for harmful

at

effect or the collateral measures necessary for the device's use?

There are a lot of ambiguities in that--

DR. EDELSTEIN: No. The answer is clearly no.

DR. POOLE: Restrictions are stated in 7b.

DR. EDELSTEIN: I would answer 7a no, 7b only upon the written or oral authorization of a practitioner licensed by law to administer or use the device, use only by persons with specific training and use only in certain facilities. All three of those. That is the current--I am a little lost here as far as--I don't want to change what the current restrictions are.

Dr. Weinstein has pointed out to me that, in the manufacturer's application, they have checked "only upon the written or oral authorization of a practitioner licensed by law to administer use of the device."

DR. WEINSTEIN: I believe that is the current restriction of the PMA device. That is the only applicable restriction in the PMA device.

[Conversation off the record.]

DR. THRUPP: To get on the record this interchange--

MR. MULDER: Ross Mulder, bioMerieux Vitek. What we have checked now are the only restrictions that are

at

currently in effect that, on the written or oral authorization of a practitioner licensed by law to administer or use the device." That is in our labeling currently.

DR. THRUPP: So even though it is class III at the moment, with a PMA, that is all that is in there. That is all that the FDA has required for these; is that correct?

MR. MULDER: CLIA will control--it is highly complex so that is controlled by the laboratory.

DR. THRUPP: So this is punted to CLIA anyway.

DR. WEINSTEIN: As a practical issue, shouldn't the next item also be checked, that is use only by persons with specific training or experience in its use?

MR. MULDER: Then you have to get into what specific training, and I don't know if it gets into all the definitions. Whereas CLIA has defined it all.

DR. ZABRANSKY: CLIA defines it there by the competency of the individuals, addresses it by proficiency testing and all that sort of stuff.

DR. THRUPP: I would think that it would be generically appropriate to have at least that second one be checked.

DR. ZABRANSKY: You need both of them.

DR. THRUPP: That is what is going to happen

at

anyway and CLIA is going to, hopefully, see to it that it is qualified labs that are using it.

DR. GUTMAN: We usually approach this through the CLIA mechanism for controlling labs. It was be rather unusual for us to restrict the device. It is not unheard of. It is possible to restrict it. But, for a complex automated system of this type, we would normally not make special restrictions but assume that laboratory practice and laboratory regulation would catch that. So we would not, necessarily, request or recommend you apply that. We wouldn't know what to do with it, frankly, in a clearance letter.

DR. THRUPP: So if it is not going to help anything, then we will get rid of it. We have done the seven questions.

DR. EDELSTEIN: Mr. Chairman, my next question is do we really have to fill out the supplemental datasheet as well?

DR. POOLE: You could do it now while Dr. Gutman makes a presentation so our consumer rep could leave.

DR. EDELSTEIN: Is it possible that we could just sign it and all agree to what it should say and have someone else fill it in?

DR. POOLE: Not all the questions are applicable.

at

The most important are 1, 2, 3, 4, 5 and 6.

DR. THRUPP: Dr. Gutman, you are wrapping this up.

**Presentation by Division Director**

DR. GATES: This is Mr. Rodriguez' last official meeting with us as our consumer rep. I can't think of a more perfect way to send him off than to have him sit through a classification panel which shows what dedication he truly has.

We are very grateful for his service with us, thank him and wish him well. I have a certificate signed by my boss's boss's boss, Dr. Burlington, which I know you will treasure.

Thank you.

[Applause.]

DR. THRUPP: Question 6, as it is worded on the supplemental sheet doesn't really say performance standards, although it did on the other questionnaire. Is priority supposed to be filled in?

DR. POOLE: No. No. 7 is not applicable.

DR. EDELSTEIN: Will it be a problem if we all write slightly different indications for use? Or shall we all agree on the language?

DR. POOLE: I think if you have a different opinion on indications for use, we should voice them out

at

loud so we can all be in agreement.

DR. EDELSTEIN: My suggestion is to refer to the manufacturer's application.

DR. POOLE: Unless it is different, you just have to state, "based on our clinical experience and judgment," unless you have other reasons why you made your recommendation.

DR. GUTMAN: You need to give your paperwork--so we will adjourn not actually until Dr. Thrupp says you can go, but if you want to sneak out, it is all right if you have finished your paperwork.

I want to take a moment to thank Dr. Thrupp. This happens to be his last panel meeting as our panel chair. He is not off the hook in that he remains on our active panel list and is likely to grace our environs again in the capacity as, hopefully, a willing volunteer on this panel. I think that explains the absence of the special certificate from my boss's boss's boss.

But the lack of certificate does not indicate a lack of appreciation for the wonderful work he has done. We not only gave him a sendoff with classification panel, we gave him a sendoff with a three-day panel all for the price of one.

He has, as always, done a marvelous job. Thank

at

you very much, Lauri.

[Applause.]

[Whereupon, at 4:15 p.m., the proceedings were  
adjourned.]