

at

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

**GASTROENTEROLOGY AND UROLOGY DEVICES PANEL  
OF THE MEDICAL DEVICES ADVISORY COMMITTEE**

**OPEN SESSION**

Friday, November 19, 1999

8:30 a.m.

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Room 020B  
9200 Corporate Boulevard  
Rockville, Maryland

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## PARTICIPANTS

Craig F. Donatucci, M.D., Acting Chairperson  
Ms. Mary Cornelius, Executive Secretary

### VOTING MEMBERS

Jenelle E. Foote, M.D.  
Robert H. Hawes, M.D.  
Joseph H. Steinbach, Ph.D.

### TEMPORARY VOTING MEMBERS

Michael S. Epstein, M.D.  
LTCDR Fathia Gibril, M.D.  
Mark A. Talamini, M.D.  
Lawrence W. Way, M.D.  
Karen L. Woods, M.D.

Diane K. Newman, RNC, MSN, CRNP, FAAN, Consumer  
Representative

Alan H. Bennett, M.D., Industry Representative

at

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P R O C E E D I N G S

**Call to Order**

DR. DONATUCCI: This is a call to order for this panel meeting of the Gastroenterology and Urology Devices Panel. I would like to note for the record that the voting members present constitute a quorum, as required by 21 CFR Part 14. Would each member introduce him or herself and designate their specialty, position title and institution, and status on the panel, starting at my far right?

DR. SCHULTZ: Good morning. My name is Dan Schultz. I am the Acting Director for the Division of Reproductive, Abdominal and Radiological Devices, and I would like to take this opportunity on behalf of the Division to welcome you all here. Thank you.

DR. TALAMINI: Mark Talamini, Associate Professor, Johns Hopkins University School of Medicine, temporary voting member for this panel.

DR. DONATUCCI: Craig Donatucci, Associate Professor of Surgery, Duke University. I am the chair of the panel for this meeting, and I will vote only in the case of a tie.

MS. CORNELIUS: Mary Cornelius, I am the Executive Secretary of the panel.

DR. HAWES: Rob Hawes, I am Professor of Medicine at the Medical University of South Carolina. I am a voting member of this committee.

DR. EPSTEIN: Michael Epstein, private practicing gastroenterologist, Annapolis, Maryland.

DR. BENNETT: I am Alan Bennett. I am a urologist and the industry representative to the panel.

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DR. STEINBACH: Joseph Steinbach. I am an engineer, biostatistician, University of California at San Diego. I am a voting member of the panel.

DR. GIBRIL: Fathia Gibril. I am a gastroenterologist, Senior Clinical Investigator, Chief, GI Consult Service, NIH. I am a temporary voting member.

DR. WAY: Lawrence Way, Professor of Surgery, University of California, San Francisco. I am a general surgeon.

DR. WOODS: Karen Woods. I am an Associate Professor of Medicine, gastroenterologist, at Baylor College of Medicine in Houston.

DR. DONATUCCI: I will now turn the meeting over to Mary who will read the executive secretary statement.

MS. CORNELIUS: Good morning. Before we begin, I would like to read a statement concerning appointments to temporary voting status.

Pursuant to the authority granted under the Medical Device Advisory Committee charter, dated October 27, 1990, and as amended August 18, 1999, the following people have been appointed as voting members by Dr. David W. Feigal, Jr., Director of the Center for Devices and Radiological Health, for this panel meeting of the Gastroenterology and Urology Devices Panel Michael S. Epstein, Dr. Fathia Gibril, Dr. Mark Talamini, Dr. Lawrence Way and Dr. Karen Woods.

The following announcement addresses conflict of interest issues associated with the meeting and is made part of the record to preclude even the appearance of impropriety. Conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants and has determined that no conflict exists.

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

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

Dr. Donatucci will ask all persons making statements, either during the open public meeting or during the open committee discussion portions of the meeting, to state their name, professional affiliation, and disclose whether they have any financial interest in the medical device company.

Finally, I would like to remind you that the tentative year 2000 panel dates are January 27 and 28, April 13 and 14, August 31 and September 1, November 30 and December 1. If the panel meeting is going to be held, I will notify you at least two months in advance of the meeting. Please, if you have changed your title, position or address, could you provide me with this information by way of an updated CV? And, if you have an e-mail address, it would be extremely helpful.

DR. DONATUCCI: We will now proceed with the open public hearing session of this meeting. I would ask at this time that all persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of the meeting. Before making a presentation to the panel, state your name and affiliation, and the nature of your financial interest in that company.

Let me quickly remind you that the definition of financial interest in a sponsor company may include compensation for time and services of clinical

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investigators, their assistants and staff in conducting the study and appearing at the panel meeting on behalf of the applicant, direct stake in the product under review, that is inventor of the product, patent holder, owner of shares of stock, etc., owner or part owner of the company. Of course, no statement is necessary from employees of that company.

I would ask that all persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of the meeting. Before making your presentation to the panel, state your name and affiliation and the nature of any financial interest you may have in the topic you are going to present.

We will now proceed with the first open public hearing of this meeting. Is there anyone wishing to address the panel? Please raise your hand, and you may have an opportunity to speak.

[No response]

As there is no request to speak, I will call to order the open committee discussion. I would like to remind public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

The first speaker, as listed on the agenda, is Dr. Kimber Richter, Deputy Director, Office of Device Evaluation

### **Open Committee Discussion**

DR. RICHTER: Thank you. I would like to begin by introducing the Center Director. Dr. David Feigal has joined us, the Center Director for CDRH, the Center for Devices and Radiological Health. Dr. Feigal?

DR. FEIGAL: Thank you very much. I would like to begin by just saying how much we, at the Center, appreciate the work of the panel and those that are willing to

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serve on this panel. Advisory committees were actually my first introduction to the FDA when, as an investigator at the University of California, San Francisco, I was asked to come and present a study to an advisory committee on a new drug application. The next thing I knew, I was a member of a committee and, not long after that, joined the agency. So, I just mention that as a warning to you --

[Laughter]

-- that one thing can lead to another! But we very much appreciate the opportunity to have a public forum to present innovations, the challenges of evaluating those innovations, and moving products rapidly to market, and identifying the kinds of issues that need to be addressed and those that need to proceed with a little more caution. So, thank you very much for your efforts.

DR. RICHTER: The FDA would also like to take this opportunity to recognize two panel members, Dr. Alan Bennett who has provided support to the Gastroenterology and Urology Devices Panel for the past seven years. Dr. Bennett is a urologist and he began in 1992 as a panel consultant. At that time, he was a professor of surgery and head of the division of urological surgery and vice chairman of the department of surgery at Albany Medical College. After that time he began a second career with C.R. Bard and has served now on the panel as the industry rep., and I understand that this is your last panel meeting --

DR. BENNETT: I just found that out --

[Laughter]

-- so, I don't have to worry about these dates in year 2000.

DR. RICHTER: Well, we have an award for you and would like to thank you for your efforts. Would you mind coming here?

DR. BENNETT: Thank you.

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DR. RICHTER: Thank you very much.

[Applause]

The FDA would also like to recognize Dr. Leonard Vertuno for his dedicated support of the Gastroenterology and Urology Devices Panel over the last eight years. Dr. Vertuno is a nephrologist who was the chief of staff and associate dean for professional affairs at Foster McGraw Hospital at Loyola Medical Center, in Illinois, and, unfortunately, Dr. Vertuno couldn't be here today because he is recovering from surgery. So, we are sending him our best wishes for a speedy recovery and also our appreciation for his work.

DR. DONATUCCI: Thank you, Dr. Feigal and Dr. Richter. I would like to remind the panel that they may ask for clarification of any points included in the sponsor's presentation but discussion should not go beyond clarification. The first speaker for the sponsor is John Yager.

### **Sponsor Presentation**

#### **Introductory Remarks**

MR. YAGER: Good morning. My name is John Yager, and I am director of regulatory affairs and quality assurance for SpectraScience.

[Slide]

On behalf of SpectraScience, I would like to thank you for giving us the opportunity to present the results of our Phase II clinical trials for our Optical Biopsy System.

As will be seen in our presentation of the Optical Biopsy System, it is a laser induced autofluorescence spectrophotometry system that, when used as an aid during endoscopic examination of the colon, increases the sensitivity of the endoscopist in the classification of adenomatous polyps.

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[Slide]

The information that will be discussed today is based on the efforts of SpectraScience over the last 18 months to develop and evaluate the effectiveness of the Optical Biopsy System.

The clinical study was designed by SpectraScience and reviewed by FDA in April of 1998 to ensure that the clinical hypothesis was appropriate and that the sample size for the study provided appropriate statistical power and significance. Based on FDA's review from the April, 1998 meeting we proceeded with our Phase II trials for the Optical Biopsy System.

[Slide]

The clinical hypothesis that was tested in our Phase II trials was to evaluate the sensitivity of the Optical Biopsy System assisted endoscopy to correctly classify adenomatous polyps and compare the results to the sensitivity of unassisted endoscopy.

Stated statistically, our null hypothesis was that the sensitivity of Optical Biopsy System assisted endoscopy would be equal to the sensitivity of unassisted endoscopy, and that the alternative hypothesis would be that the sensitivity of Optical Biopsy System assisted endoscopy would not be equal to the sensitivity of unassisted endoscopy.

[Slide]

Assuming that the alternative hypothesis could be proven, SpectraScience proposed that the indications for use statement for the Optical Biopsy System would be that the Optical Biopsy System be used as an aid during endoscopic examination of the colon to classify adenomatous polyps that are less than or equal to 1 cm; that the Optical Biopsy System be used as a supplement, and not replace, the clinical judgment of the

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physician; and that an increase in the ability to identify potentially adenomatous polyps can be obtained using the Optical Biopsy System when a suspicious finding is obtained by either the clinical judgment of the physician, the results of the Optical Biopsy System, or both the physician and the Optical Biopsy System.

[Slide]

I would now like to take the opportunity to introduce those individuals from SpectraScience who are with me today and will be addressing the panel. First, Mr. Chet Sievert, who is the president and chief executive officer of SpectraScience, and also Mr. Ron Zimmermann, who is the director of engineering for SpectraScience.

[Slide]

Also with us today and representing SpectraScience are Dr. John Bond. Dr. Bond is Professor of Medicine at the University of Minnesota and is Chief of the GI Section at the VA Medical Center in Minneapolis, and past president of the American Society for Gastroenterology Endoscopy, and is a recognized expert in the field of colonoscopy and colorectal cancer screening. He is also the author of the current American College of Gastroenterology and guidelines for the management of patients with polyps. Dr. Bond is a medical advisor for SpectraScience.

Dr. Ken Wang is the primary investigator from the Mayo Clinic who participated in our clinical study. Dr. Wang is Associate Professor of Medicine at the Mayo Clinic School of Medicine and is also head of the Advanced Endoscopy Unit at the Mayo Clinic.

Dr. Stephan Norsted is a regulatory and clinical consultant for SpectraScience, and is an epidemiologist by training.

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Finally, Dr. Douglas Hawkins is Professor and Chairperson of the Department of Applied Statistics at the University of Minnesota, and is the statistical consultant for SpectraScience.

[Slide]

Our presentation of the Optical Biopsy System and our Phase II clinical trials will begin with Mr. Ron Zimmermann, providing you with a description of the Optical Biopsy System and its features. The Dr. Norsted will provide you with a discussion of the clinical study hypothesis, clinical study design and our intended analyses of the Phase II clinical data. After Dr. Norsted has framed the clinical study hypothesis and the scope of our clinical study, Dr. Wang will present the results of the study.

[Slide]

Following Dr. Wang, Dr. Bond will provide you with a discussion of the current practices and guidelines related to endoscopy of the colon and the future challenges facing the endoscopist. Following Dr. Bond, Mr. Sievert will present a summary of our presentation.

Now I would like to turn the podium over to Mr. Zimmermann who will begin our presentation.

### **Device Description and Characteristics**

[Slide]

MR. ZIMMERMANN: My name is Ron Zimmermann. I am the director of engineering with SpectraScience. I will be speaking about the device characteristics and giving a description of our Optical Biopsy System.

[Slide]

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The Optical Biopsy System uses laser induced autofluorescence of tissue to differentiate between tissues of different morphologies. The laser induced fluorescence technology used measures the tissues own native fluorescence, which does not require any pretreatment such as dyes or photosensitive drugs.

To accomplish this, our proposed system uses a spectrophotometer which is the same technology used in clinical chemistry today. There are many different types of commonly used spectrophotometry such as reflectance, time resolved, elastic scattering and fluorescence that have been used in medicine for many decades.

Our proposed application merely takes spectrophotometry out of clinical chemistry and into the examination room for real-time use. The unique and proprietary product development SpectraScience has accomplished is the development of a statistical algorithm to interpret the recorded signal and deliver a result.

[Slide]

Previous work performed by Dr. Alfano of MIT identified certain fluorophors and their respective signature wavelengths as shown here.

As seen in this chart, each fluorophor has a unique shape based on intensity and wavelength. The spectral signature of these fluorophors from tissue combines into one spectral image used to evaluate a sample. Retrospective clinical studies utilizing these fundamental discoveries have been performed by several prominent gastroenterologists include Overhold and Vo-Dinh of Oak Ridge National Laboratory, Nishioka and Schomaker of Massachusetts General Hospital, Sivak and Van Dam of the Cleveland Clinic, and the Kapadia group of Yale University School of Medicine.

These previous studies had similar protocols and endpoints to the SpectraScience clinical studies. All studies focused on the endpoint of the sensitivity to

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distinguish an adenoma. All studies considered the clinical utility to be the real-time distinction between hyperplastic and adenomatous polyps.

[Slide]

As a result of our Phase I study, we show here that the green spectral trace represents the combination of fluorophors for a hyperplastic polyp and the red spectral trace represents the combination of fluorophors for an adenomatous polyp.

[Slide]

The Optical Biopsy System includes the system console and optical biopsy fiber. This is a picture of the console, on the left, and the optical fiber which is combined with the accessory forceps. The optical fiber connects to the front of the system console and is passed through the working channel of the endoscope.

[Slide]

The Optical Biopsy System console includes a laser and spectrophotometer, computer control module, display and keyboard, power supply, and proprietary software application. With the exception of the proprietary software application, they are off-the-shelf and commonly used components.

[Slide]

This is a drawing of the optics configuration of the system. A laser excitation source is launched into an optical coupler, which is here. The optical coupler delivers the light energy through the optical fiber to the tissue and delivers the return signal from the tissue through the coupler to the spectrograph which images the signal on the detector.

[Slide]

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The computer subsystem consists of a Pentium class computer that is year 2000 compliant, the Windows 95 operating system, and our proprietary software application.

[Slide]

The proprietary software application controls the function of the Optical Biopsy System. In controlling the system, the software performs self-diagnostics and real-time quality control of the spectral signal. When the system is powered on, the software performs power-up diagnostics that verify the system performance prior to a procedure starting. Next, the software calibrates the system and the optical fiber and verifies the system's optical properties are within design specifications.

[Slide]

After the calibration is complete, the fiber is put through the working channel of the endoscope and contact is made with the polyp. The user then depresses the footswitch to start the tissue acquisition that collects and records the spectral data.

During the collection of the spectral data, real-time verification of the data is performed to ensure tissue contact. The system will not operate if the fiber is not in proper contact with the tissue. This is followed by the analysis of the spectral data which outputs the results to the user in the form of an icon.

[Slide]

This is a picture of a display from the Optical Biopsy System. The user interface is designed for ease of use. The system control is based on 5 menu selections, on the top here, that include "begin procedure" that starts a procedure for each patient; "new specimen" that prepares the system for the next polyp, "new device" that allows the user to replace the optical fiber if damaged or if it fails calibration, "end procedure" that

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allows the user to end the current procedure, and "archive data" that allows the user to archive the spectral data on a removable disk.

A dialog box, on the bottom here, prompts user actions for each step of the procedure. The procedure summary area displays the spectral data sets that are used for analysis. The analysis results are displayed in the form of an icon, red or green icon, that requires no user interpretation. This plot area, this open area, is used for scientific studies when display of the acquired signal is required.

[Slide]

During an actual Optical Biopsy System usage, the endoscopist observes a polyp; they position the optical fiber on the tissue; they depress the footswitch to collect the spectral data; and view the analysis result as an icon stating "suspect" or "not suspect." The icon represents an evaluation result and is not a diagnosis. We will present the decision-making matrix on how to use this adjunctive information later in the presentation.

[Slide]

This is a picture of the optical fiber combined with an accessory forceps. The single optical fiber connects to the system and acts as a light wave guide from the laser to the tissue and back to the spectrophotometer. The accessory forceps facilitates the optical fiber positioning and the ability to perform a physical biopsy and/or polypectomy without introducing additional accessories. The fiber/forceps combination is compatible with either flexible sigmoidoscopes or colonoscopes.

[Slide]

The Optical Biopsy System and optical fiber have been tested based on appropriate national and international standards to ensure that they do not affect nor are affected by other equipment, and to ensure they do not pose a safety risk to the user. This

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includes electrical immunity, emissions, and safety testing as appropriate for FDA and CE mark requirements, laser safety testing that ensures no eye protection is required, and biocompatibility testing to ensure that the optical fiber is safe for use as defined in the proposed labeling.

[Slide]

In compliance with QSR regulations, verification and validation testing has been performed to ensure the optical biopsy system meets the design requirements specified for the device. The Optical Biopsy System and fiber were designed and developed under design control regulations stated in QSR and ISO regulations, and the Optical Biopsy System and fiber shall be manufactured according to these regulations.

[Slide]

In conclusion, the Optical Biopsy System and fiber were designed for ease of use, meaning no special computer skills or data interpretation skills are required. No special endoscopic techniques will be required to utilize the Optical Biopsy System. The Optical Biopsy System meets the requirements of recognized national and international standards for product safety, and the Optical Biopsy System meets the requirements of a Class I laser device.

[Slide]

Also, SpectraScience believes that reasonable care has been taken in the design, engineering and production of the Optical Biopsy System console and fiber, and we believe that based on the manufacturing processes used, these products will function according to their design specifications.

[Slide]

I would like to give the presentation now to Steve Norsted.

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DR. NORSTED: Good morning, and thank you for the opportunity of being here. My name is Steve Norsted. I am the president of the Regulatory and Clinical Research Institute. I serve as a paid consultant to SpectraScience, Inc. However, I do not have an equity position within the company.

During the next 15 minutes I will be presenting a summary of the study design and methods of analysis that were used during the Phase II clinical study of the SpectraScience Optical Biopsy System. Following my presentation, Dr. Wang will summarize the respective results and present the clinical conclusions that have been drawn from this study.

[Slide]

Based upon the clinical need for improvement in the methods for identifying potentially adenomatous polyps, SpectraScience has developed the Optical Biopsy System for the following intended use: The SpectraScience Optical Biopsy System, Model OBS/L, is to be used as an aid during endoscopic examination of the colon to identify polyps less than or equal to 1 cm that may warrant further diagnostic evaluation. The OBS/L is intended to supplement, and not replace, the clinical judgment of the physician in determining which colonic polyps should undergo resection or biopsy for histological examination.

An increase in the ability to identify potentially adenomatous polyps, that is screening sensitivity, can be obtained using the OBS/L when the decision to submit a polyp less than or equal to 1 cm for further diagnostic evaluation is based upon a suspicious finding by either the clinical judgment of the physician, the OBS/L, or both the physician and the OBS/L.

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The following points should be underscored: First, it is not the intent of the Optical Biopsy System to serve as a stand-alone diagnostic tool. Its purpose is to identify polyps that warrant further diagnostic evaluation.

Second, because the Optical Biopsy System only measures one aspect of the polyp, that is, its spectral pattern, it does not evaluate all characteristics of a polyp that may be of relevance to the endoscopist. Therefore, the Optical Biopsy System is not intended to replace the endoscopist's assessment but, rather, to serve as an independent adjunctive tool.

Third, the indication for use statement emphasizes that an increase in sensitivity in identifying potentially adenomatous polyps will be obtained only when a polyp is considered suspicious by either the Optical Biopsy System, the endoscopist or both.

[Slide]

Based upon the intended use of the Optical Biopsy System, the following study hypothesis was developed. It was our objective to assess whether the sensitivity of an endoscopist in identifying potentially adenomatous polyps would be increased by adding to his or her visual assessment the polyp classification of the Optical Biopsy System. Our null hypothesis was that the sensitivity of an Optical Biopsy System-assisted exam would equal that of an endoscopist's visual assessment. Our alternative hypothesis was that the sensitivity of the Optical Biopsy System-assisted exam would differ from that of an endoscopist alone.

While not explicitly stated as part of the hypothesis, SpectraScience understood the practical implication that an increase in sensitivity could not be accompanied by a dramatic reduction in specificity.

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The study design selected for this investigation is that of a paired experiment. That is, multiple measurements would be made on the same study subject. A single tissue sample would be classified as hyperplastic or adenomatous by the Optical Biopsy System, an endoscopist, as well as two independent pathologists.

The method of analysis which is used to evaluate disease screening programs was adopted since it is the appropriate approach to address the study hypothesis. For example, estimates of sensitivity and specificity would be calculated using a consensus diagnosis of the two pathologists as the gold standard or reference method.

In addition, it was considered appropriate to assess the reproducibility of the diagnoses made by the reference pathologist since variability and histological classification is certainly known to occur.

Masking of results, which was often termed blinding in early scientific publications, was implemented at several points in the protocol to prevent study personnel from being biased by knowledge of the tissue classification by either of the investigators or the Optical Biopsy System.

[Slide]

During the patient examination, the endoscopist was prevented from seeing the tissue classification by the Optical Biopsy System. The institutional pathologist was prevented from seeing the tissue classifications rendered by the endoscopist as well as the Optical Biopsy System. The reference pathologist was not informed of the tissue classifications of the Optical Biopsy System, the endoscopist or the institutional pathologist.

[Slide]

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Based upon the study hypothesis, it was deemed appropriate to enroll patients with the following characteristics: It was necessary to identify patients who had been diagnosed as having one or more polyps since the purpose of the study was to assess whether the Optical Biopsy System could distinguish between hyperplastic and adenomatous polyps. Enrolling patients without polyps would provide no useful information on device performance since such patients would not be evaluated by the device.

Furthermore, it was not the purpose of this study to determine whether screening programs for colon cancer are of public health value. The clinical utility of colon cancer screening programs have been well established.

It is important to note that no attempt was made to enroll patients having polyps with certain clinical characteristics. All polyp types were to be evaluated using the Optical Biopsy System.

[Slide]

Based upon these considerations, the following inclusion/exclusion criteria were adopted. For the inclusion criteria, the patient was presenting for routine colonoscopy and, at the time of presentation, was willing to provide informed consent. During such examination, the patient must be identified as having one or more polyps and at that point would be considered formally enrolled.

Exclusion criteria included coagulopathy or other conditions which would contraindicate endoscopy. Any conditions negating biopsy or polyp removal were also considered appropriate for exclusion. We would not enroll patients who were involved concurrently in other clinical trials, nor individuals diagnosed as having familial polyposis.

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Note that patients providing informed consent prior to colonoscopy -- only if one or more polyps were found during the procedure was a patient considered to be enrolled and patients with familial polyposis were excluded from the study due to the complexity of implementing a sampling strategy that would provide a representative sample of observed polyps.

[Slide]

The study was conducted in the following manner, patients were prepared for colonoscopy per standard institutional practices. Colonoscopy was then performed. The endoscopist would visually assess each polyp identified, and endoscopists then would record the visual classification as to whether the polyp was adenomatous or hyperplastic.

[Slide]

Samples were obtained using the Optical Biopsy System in the following manner: the protocol requested that all polyps identified during endoscopy be assessed as well one normal mucosal surface within each patient. Three different sites were optically evaluated on each polyp, as well as three sites on a normal mucosal surface. Detailed instructions were provided to the investigator specifying how study results were to be recorded. Each polyp in normal mucosal sample was uniquely identified; the location noted; and the corresponding laser sequence specified.

[Slide]

Polyp size was recorded as well as a description of the suitability of contact between the tissue and the optical fiber. The endoscopist was requested to document whether or not sampling of the tissue, that is biopsy or polypectomy was warranted based solely upon the visual assessment. No other source of information was to be considered in rendering this judgment. A biopsy was then obtained from the

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sampling site. The specimen was appropriately labeled and noted in the case report form. At the conclusion of the examination patients were considered to have satisfied all study requirements as no follow-up for purposes of this experiment were considered necessary.

[Slide]

Tissue samples were then forwarded to an institutional pathologist for histological evaluation. The resulting slides were subsequently forwarded to a reference pathologist who also reviewed and classified each sample. Any inconsistencies in tissue classification between the institutional and reference pathologists were resolved by requesting each to reread the slides in question. The reference pathologists subsequently submitted a 10 percent random sample of all slides in a masked manner so that we could assess the reproducibility of tissue classifications.

[Slide]

I will now summarize the methods of analysis proposed in the investigational plan.

[Slide]

The first step in the analysis was to obtain a histological classification for each tissue sample which was agreed to by the institutional and reference pathologist. The second step was to apply the classification rules that will be provided in the instructions for use of the Optical Biopsy System.

While the endoscopist and the Optical Biopsy System will make independent judgments as to whether a polyp warrants further diagnostic evaluation, the decision rules to be presented in the device labeling stipulate that an examination will be considered positive if either or both of these two sources consider the polyp suspicious. An examination will be considered negative only when the endoscopist's visual assessment and the Optical Biopsy System consider the polyp not to be suspicious. The

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conclusion drawn from applying these classification rules is termed "the Optical Biopsy-assisted screening result."

[Slide]

These classification rules were developed to be an integral part of the device labeling for the following reasons: As I have previously stated, since the Optical Biopsy System evaluates only one aspect of a polyp, its spectral characteristics, the device is intended to augment and not replace the visual assessment by the endoscopist. Furthermore, an increase in screening sensitivity can be obtained when a suspicious finding by either of these independent methods results in further diagnostic evaluation.

[Slide]

The next step to be performed in the analysis of the study data would be pooling of the data across investigational sites. Descriptive analyses would then be performed to characterize patient demographics as well as clinical characteristics, and frequency counts will be made of the number and proportion of polyps by type and location based upon the consensus diagnosis.

[Slide]

Estimates of sensitivity, specificity, the predictive value of a positive test, the predictive value of a negative test, and overall accuracy were to be computed comparing the consensus diagnosis independently with tissue classifications by the Optical Biopsy-assisted exam and the endoscopist's visual assessment. Since multiple polyps would be found in some patients, as well as multiple methods of tissue classification employed on the same polyp, it was necessary to use a statistical technique that would allow such inherent pairing of data. The McNemar approach would be used to test whether there were significant differences in sensitivity of detection of adenomatous polyps between the Optical Biopsy-assisted result and the endoscopist's visual exam.

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[Slide]

It was also considered appropriate to determine whether there would be a significant improvement in sensitivity using the Optical Biopsy-assisted result observed during the Phase II experiment to that of the endoscopist alone documented during the Phase I study. The endoscopist's performance during the Phase I study could be considered an objective performance criterion.

The panel pack which you have been presented includes an analysis comparing the Optical Biopsy result alone during Phase II to that of the consensus diagnosis during the Phase II experiment. That analysis was performed at the request of the Food and Drug Administration. It was not proposed as an appropriate method of analysis in the original clinical protocol and must be considered an a posteriori approach. Since that analysis is not in compliance with the proposed device labeling, which requires use of the classification rules which I previously outlined, we do not believe those results support or refute the conclusions to be drawn from this study.

[Slide]

The protocol does specify that Kappa statistics be used to assess reproducibility of histological classifications between the two pathologists, as well as for the reread of the 10 percent of slides by the reference pathologist.

[Slide]

Sample size calculations were performed to show that adequate statistical power would exist to identify significant improvement in sensitivity. Results from the Phase I study were used to provide estimates for purposes of these calculations. The results specified that a minimum of 101 tissue samples would have to be examined during the Phase II study.

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In closing, prior to initiation of this investigator SpectraScience met with representatives of the FDA on April 27, 1998 and presented the proposed hypothesis, the intended study population, choice of study design, and anticipated methods of analysis. At the conclusion of that meeting, and as documented in the meeting minutes that followed, FDA made no objections to the initiation of the study. The study was then conducted. I will now turn over the presentation to Dr. Wang, who will present to you the results of the investigator.

### **Clinical Study Results**

DR. WANG: I am Dr. Wang. I am a practicing gastroenterologist at the Mayo Clinic. My financial interests in SpectraScience were really just to conduct this study, and also some involvement in using this device in an NIH-sponsored grant to study molecular abnormalities in Barrett's esophagus. I presume I am going to be compensated for this visit, although we haven't discussed that yet. This would be a good time, I guess!

[Laughter]

[Slide]

These were the objectives and endpoints, as previously stated by Dr. Norsted, just to refresh your memories. The clinical trial was to test the clinical hypothesis that OBS-assisted endoscopy was more sensitive than unassisted endoscopy in identifying adenomatous polyps. The sample size, based on our Phase I studies, estimated we need 101 polyps to obtain a power of at least 90 percent and obtain significance levels of 0.05. During the study we collected the following information: Patient demographic data, physical biopsies of each polyp, as well as a visual description of each polyp which included size, color and texture of the polyp, as well as an assessment by the endoscopist of whether or not the polyp was adenomatous or hyperplastic. Finally, after the polyp was biopsied, this was correlated with the spectral

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data obtained during the Optical biopsies. These were then compared using a 2 X 2 contingency table as previously described.

[Slide]

There were five centers that actually participated in the study, myself at the Mayo Clinic, Nor Nishioka at Massachusetts General Hospital, Ollie Cass at Hennepin County Medical Center, and then two groups that are part of the Minnesota Clinical Research Center, one in Minneapolis with John Allen, and one in St. Paul with Phil Stoltenberg.

All sites followed the same clinical protocol. All obtained IRB approval for this study. All patients gave informed consent prior to undergoing colonoscopy, and if a polyp was discovered the patient was enrolled in the trial.

[Slide]

As you can see, a total of 152 patients were enrolled in all of the 5 centers. The number of patients enrolled per site varied from 9 at Hennepin County Medical Center to 76 at the Mayo Clinic.

As reported to the FDA in the clinical study report, no adverse events were seen during the clinical study. The assessment of adverse events included both adverse events resulting from the Optical Biopsy or the endoscopic procedure itself.

As stated previously by Dr. Norsted, once the required spectral, biopsy and clinical data were collected from the patients they were considered to have completed their participation in the study and no further follow-up was conducted.

[Slide]

This just summarizes basically what happened in the study. The study initially recruited a total of 152 patients. In the validated data set there were 136. These 152 patients actually had about 190 polyps. In the validated data set there were 136

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patients -- these are the completed data sets and 177 polyps then were in this set. Then, finally, for the analysis, since we were mainly interested in polyps less than a centimeter, there were only 114 patients who met that criteria and 152 total polyps.

[Slide]

The data set validation was collated and verified. The procedures used to validate the data included verifying the integrity of the spectral data files, reviewing the case report forms for completeness and linkage to the spectral data files, and independently verifying the system algorithm output.

[Slide]

The demographic characteristics of the 152 patients are as shown above. Actually, this is only the set of the 136 that had validated data. These had an age range between 30 and 91 years, with an average of 63.9. It is important to note that the reason this dropped from the 152 is that 14 of the patients were excluded because of lack of -- well, detector failure for one; 2 additional patients were excluded because of incomplete information; and one event of device failure accounted for 14 of the patients. And 136 patients in our final data set included 82 males and 54 females.

Based on the fact that there are no known demographic determinants of significance when studying colon polyps, and based on the design of the study no additional demographic analyses were performed. A total of 177 polyps were harvested from these 136 patients, a mean of 1.42 polyps per patient.

[Slide]

This shows the pathologic classification for the study specimens. Please note that among these normal specimens were included 129 specimens that we knew were obtained from normal mucosa. We took that set in every patient that was studied from normal mucosa. Unfortunately or fortunately, 18 polyps that were classified as

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normal by the pathologist were actually seen to be polyps by the endoscopist, and that number combines together to be the 147 you see in this set.

Once the overall pathology of the specimens was determined, clinical sensitivity, specificity, positive and negative predictive values and overall accuracy was determined for endoscopy alone and also for OBS-assisted endoscopy. These analyses were conducted initially for all the specimens, for all the polyps only and, finally, for the polyps less than 1 cm.

Since the hypothesis was to assess the clinical sensitivity of OBS-assisted endoscopy compared to unassisted endoscopy in polyps less than 1 cm, we will only be discussing that subset of patients in the following slides.

[Slide]

These are for polyps less than 1 cm in size, and we are comparing unassisted endoscopy to pathology. As can be seen, the unassisted sensitivity of the endoscopist participating in our study to visually assess and identify adenomatous polyps seen during endoscopic examination of the colon was 84.3 percent. The specificity was 46 percent. The positive predictive value, about 69 percent, negative predictive value 67 percent, and overall accuracy about 68 percent. Most of these values are influenced by the false-negative category in which 14 polyps were classified as normal by endoscopy and neoplastic or adenomatous by pathology.

[Slide]

Now, if you compare the polyps less than 1 cm using OBS-assisted endoscopy to pathology in the same 152 polyps, we increase the sensitivity from the prior 87 percent to 95.6 percent. The specificity drops a little bit, from 46 percent to 42.9 percent. Positive predictive value increased from 68.8 percent to 70.2 percent. Negative

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predictive value increased from 67.4 percent to 87.1 probability, and the overall accuracy increased from 68.4 percent to 73.7 percent.

[Slide]

When the results of our study were analyzed statistically using the McNemar's symmetry analysis, a statistically significant improvement in the identification of adenomatous polyps was seen. The use of the Optical Biopsy System in addition to visual assessment of the polyps by the endoscopists participating in our study resulted in correctly identifying an additional 10 adenomatous polyps. This represented a 13.3 percent increase in the classification of adenomatous polyps. The level of statistical significance of this finding was less than 0.002.

[Slide]

Although this was not analyzed for significance, when results of unassisted and OBS-assisted endoscopy were stratified and compared by the endoscopists estimation of the polyps actual size, we can see that the OBS-assisted endoscopy aids significantly in the classification of all sizes of adenomatous polyps up to 1 cm. There was only one case of a decrease here, and that was probably just a fluke.

[Slide]

Looking at the tissue classification reproducibility or inter-observer variation among pathologists, we compared the institutional pathologist to the reference pathologist classifications. For this analysis, the kappa statistic was used to evaluate the level of agreement between the pathologists participating in the study. Inter-observer variation was assessed by comparing the results of the first reads obtained from both the institutional pathologist and the reference pathologist. Results calculated using the kappa statistic confirm that there was good agreement -- kappa was 0.9 -- between the

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pathology readings obtained from the institutional pathologist and our reference pathologist.

[Slide]

We also compared the intra-observer variation of our reference pathologist using the kappa statistic. For this analysis, a 10 percent sample of the slides was selected from the population of the slides previously read by the reference pathologist, and was re-masked and resubmitted for classification.

Based on the results of this analysis -- the kappa was 0.895, we confirmed the reproducibility of the reference pathologist for classifying tissue specimens. The results of these analyses support the use of the pathology as the gold standard for comparison in this study.

[Slide]

However, there do remain a few outstanding clinical study questions which were raised by the FDA: Did the lack of 100 percent sampling introduce bias into our study results? Also, what was the significance of the question on the case report form that asked the endoscopist whether or not he or she would sample the polyp being studied?

[Slide]

Was bias introduced by less than 100 percent sampling? It is the position of SpectraScience that based on the fact that there are many variables encountered during the performance of endoscopy of the colon and many clinical factors influenced the clinicians involved in our study that any polyp not sampled and, therefore, not included in the study was the result of random and not systematic exclusion.

As seen from the factors that may have confounded the collection of data from all polyps seen during the study could include factors such as procedure time that

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extended beyond that planned; patient intolerance of the procedure; medication considerations; and equipment performance. Polyps were not excluded on the basis of polyp characteristics. Therefore, we believe that there was no real harmful bias introduced into the study.

[Slide]

This is the case report form and question, and this is the issue that was raised, would we normally sample the specimen.

[Slide]

A response to the question on the case report form to sample was not intended as a study endpoint. The question which was raised by the FDA created some confusion and discussion regarding the appropriate endpoints of our study. Scientifically, we feel that the use of this information to assess the clinical utility of OBS-assisted endoscopy is problematic. Since the results of the OBS were masked, we did not actually see whether or not the machine classified the polyps as either adenomatous or hyperplastic, and no adjunctive information was available to the endoscopist. We don't understand why anyone would not expect the endoscopist to sample these lesions to obtain additional information so they could make appropriate treatment decisions.

[Slide]

The definition of sample as intended by SpectraScience to be used by the endoscopists in our study was whether or not they would biopsy or perform polypectomy and submit the tissue to pathology to obtain additional information before making treatment decisions for these patients.

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The results of our Phase II clinical trials support our clinical hypothesis that the sensitivity of Optical Biopsy-assisted endoscopy is more sensitive than unassisted endoscopy for the classification of adenomatous polyps.

Furthermore, we believe that the data presented represent valid scientific evidence to support the proposed clinical utility, and the data provides reasonable assurance of the effectiveness of the Optical Biopsy System for its intended use.

[Slide]

Thank you. Now Dr. Bond will be presenting the clinical practice and guidelines.

### **Clinical Practice and Guidelines**

DR. BOND: Thank you very much. I would like to start off by saying that I have had no role in the development or the testing of the Optical Biopsy System. I have no equity interest in this company or any other device company, other than that I do expect to be compensated for the time that I have spent as an advisor to the company.

I have been asked to advise primarily on the intended use of the Optical Biopsy System in clinical practice, not only in terms of what we have done in the past in the management of polyps, but what current trends and guidelines are indicating the future of our practice in our area is likely to be.

My credentials for doing that, I guess, are mainly that I have worked most of my career in the area of colonoscopy, endoscopy of the lower GI tract in the management of patients with polyps and screening for colon cancer and for colorectal polyps. In addition to what was mentioned by Mr. Yager earlier, I served as director of one of the centers for the national polyps study, the U.S. National Polyps Study, which probably is the main scientific trial from which we have derived most of our clinical practices.

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In addition to that, I was a co-principal investigator in the large Minnesota fecal complex screening trial, and currently am a co-director of a center both for the VA colonoscopy screening trial which is ongoing and for a newly sponsored National Cancer Institute pilot study to see if we can mount a national colonoscopy screening trial in the United States.

[Slide]

Also, I was fortunate or honored, I guess, to be asked to conduct or to put together or develop the single major evidence-based guideline that gastroenterologists now use in this country to aid in the management of their patients with the common problem of colorectal polyps. Although I was the author and the director of the project, this guideline was mounted by the American College of Gastroenterology under the auspices of its Practice Parameters Committee.

I want to emphasize that the guideline, which is very comprehensive, initially published in The Annals of Internal Medicine, in 1993, was reviewed at that time by a large multi-disciplinary panel of expert reviewers, including not only gastroenterologists but pathologists, surgeons, radiologists and oncologists. That guideline has now undergone a second revision and it will be published very soon in The American Journal of Gastroenterology in early 2000.

In addition, we had major feedback at the time this guideline was finished and promulgated from clinicians, both in gastroenterology and in primary care, in order to have their input since they are the people that are using the guideline recommendations.

[Slide]

Now, as we see it and as I see it, anyway, I think the primary value of the Optical Biopsy System is listed here, and that is to assist the endoscopist performing

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either flexible sigmoidoscopy or colonoscopy in distinguishing at that time, real-time, between small adenomatous polyps which have some relevance to colorectal cancer and the very common hyperplastic polyps which have no clinical significance.

This is an enormous clinical issue, as I will point out, since it is now recommended that all people over the age of 50 be screened for colon cancer with endoscopic methods. Some 70 million people potentially could undergo these examinations where this clinical consideration could be a major issue.

[Slide]

To give a little background for those of you who do not work in digestive medicine, colorectal cancer is a major problem in western countries, such as the United States. It is the second most common cancer killer of Americans. We have some 140,000 new cases each year and Americans now have a lifetime risk of this disease which exceeds 6 percent. It is the only major malignancy that affects not all races equally but also is the only one that affects men and women almost equally. So, 55,000 deaths occur from this disease and, although we have seen a bit of improvement, the 5-year survival from colorectal cancer is only about 55 percent, which is a tragic figure when you consider that colorectal cancer is actually one of the most preventable or treatable forms of cancer as long as it is detected early by screening.

[Slide]

Colorectal cancer is also unique among the major cancers in that over 95 percent of these cancers are preceded by a benign precursor lesion, 95 percent arise in a benign adenomatous polyp that develops and grows very slowly in the colon over many years.

We have increasingly learned, however, that we need to differentiate between the different types of adenomatous polyps that we find in practice because the

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current studies indicate that the small tubular adenomas, which are very common, estimated to exist in about 30 percent of the population, have very little risk of dedifferentiating into a cancerous lesion.

On the other hand, the few polyps that develop additional acquired genetic alterations -- these are much less common but much more dangerous and likely to dedifferentiate into a cancerous lesion. Current clinical practice is somewhat different from what we did traditionally over the years in that our efforts are now directed away from simply detecting and harvesting large numbers of clinically insignificant adenomatous polyps towards strategies that allow us to accurately, reliably detect the patients that develop the much more improvement and dangerous advanced adenoma.

[Slide]

Now, decreasing the mortality from colon cancer is really a three-pronged effort at the present time. Primary prevention, which I won't discuss, involves changing diet, adding supplements or changing lifestyle, which is very important and is an area of intense interest.

The two areas where the Optical Biopsy System plays a role, however, is in secondary prevention, and this involves selection of the right polyps in the colon, removal of the right polyps to prevent the possibility of subsequent cancer and then, of course, screening and early diagnosis not only of the advanced adenomatous polyp but of early colorectal cancers that may form and be asymptomatic at the time of detection.

[Slide]

Now, evidence-based guidelines that have been developed in the last three or four years by the U.S. Preventive Services Task Force, by the Agency for Healthcare Policy and Research, finished by a consortium of five medical and surgical GI societies and, more recently, by the American Cancer Society now recommend that all

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asymptomatic, average risk people in the United States who are over the age of 50 be offered screening with annual fecal occult blood testing, testing for small amounts of blood in the stool, and that they at the same time have flexible sigmoidoscopy, to be repeated about every 5 years.

Other options that are included in these guidelines are, instead of doing the indirect forms of screening, some patients may prefer to have direct screening with either barium enema x-rays every 5 years or direct colonoscopy, probably needed about every 10 years. These 2 options, however, have not been shown to be efficacious in a randomized, prospective trial but are supported mainly by indirect evidence only.

[Slide]

Now, what are the recommendations for clinical practice of the small adenoma? We define the small adenoma generally as an adenoma that is less than 1 cm and does not contain advanced histologic features. The important consideration, as I have already mentioned, is to differentiate between adenomas that occur, that are found during screening, sigmoidoscopy or colonoscopy, and the also very common hyperplastic polyp which has no relationship whatsoever to colorectal cancer. If a patient only has a hyperplastic polyp found on screen, they require no further examination of their colon. If it is found on sigmoidoscopy they do not need a full colonoscopy. If it is found during a screening or diagnostic colonoscopy, they do not need expensive follow-up surveillance.

On the other hand, large adenomas with advanced features or the occasional patient that has more than 2 smaller adenomas does require colonoscopy, if that had been found on sigmoidoscopy, and usually, as long as they are in good health, require long-term follow-up surveillance.

So, the ability to distinguish between a hyperplastic polyp and an adenoma has enormous clinical ramifications, not only for the individual patient but also, of

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course, as a public health measure for society when we are recommending now that 70 million people undergo these screening examinations.

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The main departure that is present in the current polyp guideline over traditional practice is that the small tubular adenoma, if only one or two of these lesions are present, especially if they only 5 mm or 6 mm or less, may require no treatment, and no further studies, and no follow-up surveillance. This is something that is increasingly being done in practice. Experienced colonoscopists have learned that these lesions are clinically insignificant and do not indicate the need for further studies.

Optical Biopsy System has been compared with the endoscopist's ability to visually characterize a polyp. This is done by looking at the polyp, determining its size and, to some extent, by looking at the texture and the color of the polyp. However, this determination has been shown to be relatively inaccurate. I would estimate that if you eliminated the issue of size one can determine the difference between a hyperplastic polyp and an adenomatous polyp clinically with accuracy only about 70 percent at best.

[Slide]

This is an example. This is a small polyp, typical polyp that may be found on screening sigmoidoscopy. This was a polyp that, when I found it, I did not know what it was. I thought it might be a hyperplastic polyp; it turned out to be an adenoma. But, by looking at a polyp such as this, we simply cannot make an accurate determination and, therefore, the assistance of the Optical Biopsy System would be dramatically beneficial.

[Slide]

This, on the other hand, shows you what an advanced adenoma looks like. Here, there is no question. These are lesions that are very dangerous, have to be removed and there is no difficulty in making that determination visually.

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[Slide]

So, in summary, the potential benefit of an adjunctive screening tool such as the Optical Biopsy forceps is to provide real-time, during screening sigmoidoscopy or colonoscopy, to provide the endoscopist to make a determination at that time or whether or not a small lesion is hyperplastic or an adenomatous polyp. This determination would obviate the risk of doing biopsy which, although it is small, when multiplied by the number of times this is done clinically does result in considerable morbidity in the United States today. Certainly, the expense of doing a biopsy, which is enormous when multiplied times the number of times this would need to be done.

And, I would like to emphasize also that the ability to determine this real-time -- the delay of diagnosis of a biopsy creates major anxiety and affects the patient's well being, I think, of persons that undergo screening. If you consider yourself having a screening test, having something found, and then being told that in a week or two we will let you know if this is important or not important, that creates major anxiety and affects the outcome of the patient and the quality of life.

Very importantly, as Dr. Sacks has indicated in one of his recent memos, this may in a major way impair compliance with our screening recommendations. So, the Optical Biopsy forceps, I think, would be of great value in allowing immediate determinations of whether the patient has a lesion that may be related to colon cancer or if they have a hyperplastic polyp with absolutely no significance.

[Slide]

Now, the sensitivity of the visual determination plus the Optical Biopsy System approaches that of pathology, which is not perfect; it is not a gold standard. But, I would like to finish by pointing out that the significance of the small adenoma is so negligible that an occasional error in diagnosis has almost no significance. The small

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tubular adenoma has negligible prevalence of high-grade dysplasia or cancer. There is no increased risk of subsequent cancer in long-term follow-ups of patients with these small lesions. There is very little risk -- the national polyps study showed this -- of subsequent advanced adenomas developing in these patients, and recent studies have clearly shown that the finding of one or two small tubular adenomas is not an indication for full colonoscopy. It does not predict the presence of significant proximal lesions.

[Slide]

Finally, I would like to conclude by pointing out the fact that in December of 1998 the American Digestive Health Foundation conducted, together with the NIH, a workshop on endoscopic research and development priorities. The workshop was designed to identify priorities that should be developed soon, should be implemented soon that would have a major impact on clinical practice today.

I chaired the section on the colon, colon polyps and cancer, in the session. We came out with two recommendations, the second one of which was that techniques need to be developed that can distinguish hyperplastic polyps from adenomas, that this would be an extremely valuable tool during screening examinations. Thank you very much.

[Slide]

Now Mr. Sievert will summarize, I believe.

### **Summary**

MR. SIEVERT: Thank you, Dr. Bond. I plan to just kind of summarize what we have heard today and, hopefully, try to streamline this and make it quite simple because we think it is.

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As we have seen, this is our system. It is not that much more unusual or very typical to most electrosurgical generators that most of you use clinically. We do operate the equipment with the footswitch. The fiber and the forceps are connected here, at the front, of the console. It really acts muck like -- there is almost the same footprint here in size. We are a little taller. But, it will operate very similarly to an electrosurgical generator, although this is even a little simpler because there are no adjustments to be made; there are no knobs to control; there are no settings to worry about; and it is very self-directed.

It does perform a real-time analysis. Once the polyp is touched by the fiber and the footswitch is depressed, you get an analysis on the screen that Ron showed you in less than a second.

The optical scan could potentially treat with the same accessory. We have a fiber here where we can make an instant diagnosis or instant evaluation, I should say, and we can very rapidly follow and take a physical biopsy or, if the machine says that it is suspect and should be removed and the endoscopist agrees, it can be removed during the same procedure. No exchanges will be necessary because everything is built in the same accessory.

[Slide]

As we presented, the intended use for the OBS is to be used as an aid or as adjunctive information to the endoscopist to distinguish between hyperplastic and adenomas. Our clinical hypothesis logically fits as an appropriate hypothesis to test an adjunctive tool. That is, to test whether the combination of the Optical Biopsy System and the endoscopist was more sensitive than the endoscopist alone.

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Our clinical trials were designed with input from the FDA to validate or invalidate our hypothesis. Therefore, we comparatively tested the sensitivity of the endoscopist plus the Optical Biopsy System to the sensitivity of the endoscopist alone.

As Dr. Bond described, the American College of Gastroenterology guidelines state that once a polyp is discovered a visual assessment by the endoscopist for size, color and texture is the first step to determine the best course of treatment. Since it is at this juncture, right here, that the Optical Biopsy System is intended to provide objective adjunctive information to the endoscopist, to only then determine the best course of treatment. The endoscopist's visual assessment logically serves as the only appropriate endpoint to study that would appropriately test and, therefore, the endoscopist's visual assessment was added to Optical Biopsy sensitivity to compare against the endoscopist alone.

[Slide]

The results of our clinical trials were pretty simply. It validated our clinical hypothesis that the Optical Biopsy System assisted endoscopy, significantly improved the endoscopy sensitivity to distinguish between hyperplastic and adenomatous polyps.

[Slide]

We presented the results of our clinical trials that supported our original hypothesis. As Dr. Bond described, it is very important to determine whether a small polyp is hyperplastic or an adenoma. The American College of Gastroenterology guidelines state that if a polyp is greater than a centimeter, remove and send to pathology. However, if it is less than 1 cm and known to be hyperplastic, no intervention is warranted. Distinguishing between hyperplastic and adenomatous polyps is also critical information in order to recommend the appropriate surveillance recommendations by the

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physician. If it is an adenoma, surveillance is more frequent; if it is hyperplastic, less or none.

Also, as stated by GI Endoscopy Society, a hyperplastic polyp is not an indication for colonoscopy. The clinical significance of an adenoma, even if it is left behind, is really at less risk than a colonoscopy to harvest a normal polyp. If you consider the complication rate of a colonoscopy at 3 percent, consider the prevalence of an adenoma to become a cancer at 0.25, I think where everybody is trying to get to is avoiding some unnecessary colonoscopy to remove normal tissue.

[Slide]

There are many federal societies that we have quoted today on the clinical significance of hyperplastic polyps. This is just one more of those. The quote here is from the U.S. Department of Health and Human Services Colorectal Screening Manual. They concur with most of the leading experts in this field as to the significance of hyperplastic polyps.

[Slide]

As we have described, we think this device is very easy to use. It is not very complicated. It has a lot of on-board diagnostics. The software here calibrates the system to each fiber optic probe. It also operates with self-diagnostic study if there is operator error, meaning if there is movement, if there is sliding on the polyp or they have poor contact the machine will not operate and will not collect data. We have tried to take as much operator technique error out of this as we possibly could.

I think as we have described, our results have proved and validated our original clinical hypothesis and really it has been quite simple. We tested whether or not we could aid and improve the endoscopist's sensitivity to distinguish between small hyperplastic and adenomatous polyps, and I think the results are pretty plain.

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I think Dr. Bond has done a great job in describing the medical need for this particular technology. There have been a lot of articles in the last ten years in the journals of gastrointestinal endoscopy that keep talking about the need for an adjunctive tool to determine whether a small polyp is hyperplastic or adenoma.

As Dr. Bond also briefly mentioned, at a recent NIH workshop, workshop sponsored by NIH and the American Digestive Health Foundation, nationally recognized experts from the field of gastroenterology identified several key areas of clinical practice where new endoscopic technologies could enhance the current quality of care. I will give the reference to Dr. Bond's slide as published in The Journal of Gastrointestinal Endoscopy, volume 49, pages 83-84, 1999, which stated, in quotes, techniques which could distinguish hyperplastic (non-malignant) polyps from adenomas would be a valuable tool during screening examination. The article further went on to actually list several new promising technologies that accomplished this. LIF, as we call it, laser-induced fluorescence, was one of those specifically pointed out by this workshop as something that would potentially provide a good, useful clinical tool.

We hope we have presented today the pretty simple approach. We feel that we have identified the medical need for determining what these small polyps are, and we have presented some good results that would significantly improve the endoscopist's first step at evaluating small polyps. I think it fit very well with our clinical hypothesis, our clinical designed and was all very focused on the hyperplastic versus adenoma question. That is the end of my presentation.

DR. DONATUCCI: Thank you. Are there any members of the panel who would like to ask a brief question for the purpose of clarification before we take a 15-minute break?

DR. STEINBACH: Steinbach would.  
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DR. DONATUCCI: Please.

DR. STEINBACH: Mr. Zimmermann, your menu says how the operator can store data. How does he retrieve the patient data?

DR. DONATUCCI: Could you come up to the microphone, please, and please identify yourself again.

MR. ZIMMERMANN: Ron Zimmermann, director of engineering with SpectraScience. To transfer the data from the system is accomplished by the archive that stores the data on a removable device that you can take away from the system for whatever purpose, and we use that for transmitting our data from the system to our office for analysis.

DR. STEINBACH: So, there is no way that the practicing physician can access that data?

MR. ZIMMERMANN: Not directly.

DR. DONATUCCI: Yes, Dr. Epstein?

DR. EPSTEIN: Also a question for Dr. Zimmermann. Mr. Sievert said that this was about the size of an electro-surgical unit. Was he saying that this is an electro-surgical unit as well?

DR. ZIMMERMANN: No, it is not.

DR. EPSTEIN: So, you cannot perform a hot biopsy to remove a polyp?

DR. ZIMMERMANN: That is correct.

DR. EPSTEIN: Thank you.

DR. WOODS: Can you tell me the stiffness of the laser fiber that comes out from the forceps, and is there any control in place so that the fiber extends out only a certain distance or not?

DR. DONATUCCI: Please talk into the microphone.

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MR. ZIMMERMANN: I guess on the stiffness, I don't have a number or an evaluation of how stiff it is. It slightly protrudes through the end of the forceps.

DR. WOODS: So, is there a control over how far the endoscopist can advance?

MR. ZIMMERMANN: It is fixed.

DR. WOODS: So, there is no risk of it going out too far and through the wall of the bowel?

MR. ZIMMERMANN: Right. That is controlled on the proximal end --

DR. DONATUCCI: Hold it, please come to the microphone if you are going to make a comment.

DR. WANG: The fiber itself is encased, and it takes the place of the spike that is normally found inside a standard endoscopy forceps. It has a similar type of stiffness to that spike.

DR. WOODS: And what is the diameter of the forceps in the open position?

MR. SIEVERT: The biopsy forceps that are used are completely standard dimensions. It is 2.5, compatible with a 2.8 channel. The jaws are standard cup size. Everything is standard forceps other than the lumen to place the fiber. The fiber is fixed. It can't go out any further, and it is actually supported -- if you look really carefully at the slide, it is supported by a hypotube. A hypotube runs the whole lumen so that you don't get kinks, you don't get breakage of the fiber. It actually supports it.

DR. WOODS: So, the fiber is removed before the tissue is taken in the forceps?

MR. SIEVERT: We have two versions. You can retract. We have one version that retracts and one version that is fixed. Just as Dr. Wang described, it

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performs very similarly to a spiked forceps and the sample, the tissue, gets treated about the same as well.

DR. WOODS: Another technical question, if you assume then, if you are using standard forceps, that the open diameter is about 8 mm, then if you are looking at polyps less than 8 mm in size and you have to take 3 readings from the polyp -- I presume you meant they pulled it away, they put it back --

MR. SIEVERT: Right.

DR. WOODS: -- you just put it back in the same place, I guess, and take the same reading again?

MR. SIEVERT: Well, you try not to but, again, the way our system is set up, if one of the three positions define an adenoma our machine will call it an adenoma. So, we are taking three readings to try -- when we first designed the clinical trial, as you know, it might have been mixed, so one just one shot in a small space -- we thought we would increase that by taking three positions on the polyp, and if any one of those call it an adenoma the icon will represent it as an adenoma.

DR. WOODS: It would be interesting to know out of the three shots did the machine agree with itself.

MR. SIEVERT: John?

MR. YAGER: As Mr. Sievert was saying, any time the device would see adenomatous tissue, if it were one of the three samples taken it would show itself as an adenoma. The presumption is that there is variation there that is showing up.

In response to your question, if I understand it correctly, Dr. Woods, it is not an internal agreement situation because you may be on a portion of the polyp that is adenomatous where, in the other readings that you take, you might be in a portion of the

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polyp that is hyperplastic. So, I am not sure I know how to answer your question as far as internal agreement.

DR. WAY: Is that verified histologically, that these variations are reflected in different histopathologic readings?

MR. YAGER: Well, we are seeing the results from histopathology for the overall reading of the device. We are not seeing them from the individual sequences.

DR. WOODS: So, it would be nice to know though -- let's say you took three readings and one out of three was positive in most cases, and two out of three were negative. That would impact upon your recommendation to the clinician using the device to make recommendations that you always take three readings, or you always take two readings, because two out of three times it may be negative when, in fact, it is an adenoma.

MR. YAGER: We are always making the recommendation that they take three readings. The device will not display a result until they do take three readings. That is implicit in our instructions.

DR. WAY: What happens when they start bleeding?

MR. YAGER: To the best of knowledge at this point, blood in the field does not have an effect on it.

DR. DONATUCCI: Dr. Talamini?

DR. TALAMINI: I have one question. Is the computer algorithm in a final state, or do you envision further refinements as time goes on?

MR. YAGER: The computer algorithm for this submission is in the final state. We always plan to have improvements and ongoing research that would help us to improve and enhance the ability of the algorithm to be more specific and more robust.

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DR. WAY: I think this question is for Dr. Wang or Dr. Bond, given the performance characteristics demonstrated in the Optical Biopsy System under circumstances of screening, what, down the line, would be the result in cancer prevention with the widespread application of this? In other words, on a population basis?

DR. BOND: I am not sure exactly how to answer that question. The best evidence of cancer prevention by taking out polyps, secondary prevention, comes from the national polyps study which found, in a long-term follow-up of some 1400 patients who had had one or more adenomas in the colon removed and the colon cleared, that the incidence of colon cancer was reduced by between 76 percent and 90 percent compared to 3 reference populations.

Clearly, in the next millennium I think our efforts are going to shift from diagnosing already developed cancers towards trying to prevent these by finding the advanced adenoma, which is the one that is likely to turn into cancer. But, in doing that, we have to be able to differentiate between hyperplastic polyps which have virtually no clinical significance and, I believe also we have to differentiate between the advanced adenoma and the common but clinically insignificant finding of one or two small tubular adenomas -- a very common occurrence. As I mentioned, they probably exist in 30 percent of the population, and we have to learn, and we are learning how to differentiate between that benign situation and the advanced adenoma which when resected prevents colon cancer. But, I think widespread endoscopic screening is likely to have a major impact on reducing the incidence of colorectal cancer altogether. We are already seeing that actually in some of the National Cancer Institute statistics, and after some 30-40 years of increase in the incidence of cancer, we are now beginning to see a decrease.

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DR. WAY: Has anybody calculated the hypothetical change in the efficacy of cancer prevention based upon the measured performance characteristics of the system in polyps that are less than 1 cm?

DR. BOND: I think the answer to that is no but that really is not the prime intended use of the system. The intended use of the system is to be able to accomplish secondary prevention by finding the advanced adenoma and resecting it, without wasting all of the resources that we have directed at this problem in simply detecting and harvesting large numbers of insignificant lesions -- certainly, the hyperplastic polyp and probably also the small adenoma.

DR. WOODS: For Dr. Bond then also, you bring up the issue that we would reduce cost and reduce complications of biopsying polyps unnecessarily. Have you done any calculations of the impact of this in terms of what you would truly anticipate the risk reduction, the cost reduction, and also looking at the missed rate, potential missed rate of clinically significant polyps? The missed rate looks like, from the data, to be about 4.5 percent of adenomas. Of course, not all of those would necessarily be clinically significant adenomas but, from the data you presented, you could probably guesstimate how many of those would have been clinically significant, and have you looked at that with this device and what impact it might have?

DR. BOND: I know that the FDA at this point does not look at cost considerations, but it is an enormous problem in this area. The cost of doing a screening diagnostic flexible sigmoidoscopy at the present time is very low. It is \$80 to \$100. It is what HCFA pays, for example. The cost of adding a single biopsy to that can increase the procedure cost by up to \$300 to \$400 in some centers. So, when you multiply out the number of these procedures that are going to be done, and the fact that at least 20 percent of the patients that have them are likely to have a small polyp, the cost considerations are

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virtually enormous. And, this is one of the reasons why the NIH conference made this one of its priority recommendations, I believe.

The downside risk of mischaracterizing a small tubular adenoma as a hyperplastic polyp -- I tried to make that point -- I believe is clinically negligible because these are such benign and inconsequential lesions. Many of them are, at the present time, not resected, especially in older patients or in patients with other risk factors. Repetitive screening, if occasionally one does grow and develop, it does so very, very slowly. It is likely to be picked up by repeated screening over the years.

So, as I mentioned, we need to find a way to not spend all our resources on finding those little insignificant polyps towards methods that will allow us to not miss or not fail to diagnose the important ones.

DR. DONATUCCI: Before you go on, I would just like to remind the panel that the purpose of the questions at the moment is to clarify the presentation. A lot of this discussion will come up subsequently.

DR. BOND: Maybe I can mention the 4 percent figure too. One should also realize that pathology is not a gold standard. The national polyp study found that the difference in interpretation, especially for the smaller adenomas, was at least in the 4 percent error range. It did get better when a reference pathologist was used and interacted with the institutional pathologist, but that is not the way it is done in real practice. So, the error rate of pathology, in my opinion, is at least that great. But, as I say, for these small lesions it is clinically insignificant.

DR. GIBRIL: Just for curiosity purpose, the OBS alone has a sensitivity of 71 percent I believe. The 30 percent missed by this device, do you know what percentage of these were villus or tubular villus adenomas?

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DR. BOND: Maybe Dr. Wang would comment. I don't believe that that data is available. The percentage of polyps, however, that are less than 1 cm that have significant villus tissue are relatively small, less than about 1 or 2 percent. So, when large numbers of these small polyps are resected, as was done in the national polyp study, the incidence of advanced histologic features was less than 1 percent, again pointing out the fact that these lesions, especially when they are smaller than 6 mm, are extremely benign.

DR. GIBRIL: So, do you think this is applicable for screening methods, using flexible endoscopy? I mean, it was studied on colonoscopy, the study we have just seen.

DR. BOND: Polyps behave in a really generic fashion, no matter where they are in the colon, and I believe that the device doesn't know whether it is in a sigmoidoscope or colonoscope. So, I don't think that there is any problem with generalizing the information to screening sigmoidoscopy. Polyps are the same. They are just being diagnosed with a longer instrument. The polyps in the right colon are the same as in the left colon, except for the fraction that are hyperplastic are somewhat less.

DR. GIBRIL: But the problem is you just showed us a slide where there was a polyp which did not look adenomatous but it was. For a patient who has only a single polyp or two polyps on flexible sigmoidoscopy, you are going to assume that is hyperplastic or, even using the device will show it is hyperplastic and you are not going to biopsy it.

DR. BOND: That is a very good question. I think in some of those cases it wouldn't make any difference because, as you mentioned, we might not do anything with that polyp anyway unless they are multiple. If they are multiple, or sometimes when they are in patients who are somewhat younger or have other risk factors, then we may

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wish to resect every single polyp even if it is small. So, the device can be very valuable in differentiating that situation from the common situation of the hyperplastic polyp which has virtually no clinical significance.

DR. GIBRIL: But you are going to miss the synchronous polyps which occur in 30-50 percent in patients who have even a single polyp.

DR. BOND: The studies have shown, as one of my slides showed, that when that has been compared with findings in the proximal colon a small tubular adenoma or even several small tubular adenomas in the left colon does not predict a higher rate of proximal adenomas compared to the average population.

DR. HAWES: A question for Mr. Zimmermann, does the technology distinguish between tubular adenoma, villus adenoma or tubular villus adenoma, or is it just adenoma or not?

MR. ZIMMERMANN: Actually, I wonder if I should defer that to John.

MR. YAGER: To respond to your question, at the present time the device responds and distinguishes only between suspect and non-suspect on the basis of a suspect being an adenoma or frank carcinoma versus a non-suspect being hyperplastic or normal.

DR. HAWES: And to extend that, can it distinguish a cancer from an adenoma or from a hyperplastic polyp?

MR. YAGER: The same answer I just gave you. It does not distinguish from adenomatous or cancerous.

DR. WAY: this wasn't presented but it is in the data pack. The question is, is there a technical explanation for the differences in the performance of the device in the different institutions? There seemed to be patterns of variation between the institutions that aren't explained to me adequately in the presentations to this point.

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MR. YAGER: Would you like us to respond to that now or wait for the open discussion?

DR. DONATUCCI: Why don't we take this question?

MR. YAGER: Okay. I would like Dr. Hawkins to address that.

DR. HAWKINS: Good morning. Dr. Douglas Hawkins. I am Chairman of Applied Statistics, University of Minnesota, and I have worked as a statistical consultant on this project. Other than consulting fees, I have no financial interest.

DR. DONATUCCI: Could you speak into the microphone a little bit closer, please?

DR. HAWKINS: Yes, indeed. The answer to that is that there are, indeed, differences in the performance of the instrument across the centers. We are not sure of the exact reason for that. The differences seen in the instruments are, in fact, a lot smaller than the differences seen among the endoscopists themselves. The instrument seems to tame some of the endoscopist variation from center to center. We do have a display of that which we may get to in the general discussion.

DR. DONATUCCI: If you wish, you can show it now.

[Slide]

DR. HAWKINS: The bar on the left, the red bar is the sensitivity of the endoscopists. We see this ranges from 100 percent at two of the centers down to the low 50s. When we add the instrument into the picture, in all cases the sensitivity goes up substantially over where it was lowest, and even where it was high it increases further.

[Slide]

If we look at the specificity, we see that the specificity in center three is really poor, in center five was very good. Adding the instrument into the picture in all cases cost some specificity but very little.

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So, the conclusion that comes out of this, I believe, is that the center-to-center differences in the instrument are real, but they are a very small part of the total picture when we look at the endoscopist and the system operating together.

DR. DONATUCCI: Thank you. At this point, I would like to take a 15-minute break. We will reassemble exactly at 10:45. Thank you.

[Brief recess]

DR. DONATUCCI: The meeting will now reconvene with the open committee discussion. Again, I would like to remind the panel that they may ask for clarification of any points included in the FDA presentation but discussion should not go beyond clarification.

The first speaker for the FDA is Elias Mallis, electrical engineer who will provide background information.

## **FDA Presentation**

### **Background**

MR. ELIAS: Good morning.

[Slide.]

For this section of the panel meeting, I will provide you with some background of FDA's review of the Optical Biopsy System, a new device from SpectraScience, Inc. As you have already heard from the sponsor, the device system utilizes the principle of autofluorescence to distinguish between hyperplastic and adenomatous polyps in the colon.

[Slide.]

FDA's review of the premarket approval application considered the safety and effectiveness of the device system in terms of the proposed indications for use. The indications, as currently defined by the sponsor, are as follows: The OBS is intended for

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use as an aid during endoscopic examination of the colon to identify polyps less than or equal to 1 centimeter that may warrant further diagnostic evaluation.

[Slide.]

The OBS is intended to supplement and not replace the clinical judgment of the physician in determining which colonic polyps should undergo resection or biopsy or histological examination.

[Slide.]

An increase in the ability to identify a potentially adenomatous polyp--that is, the screening sensitivity of the endoscopic examination--can be obtained using the OBS when the decision to submit a polyp less than or equal to 1 centimeter for further diagnostic evaluation is based upon a suspicious finding by either--

[Slide.]

--the clinical judgment of the physician, the OBS or both the physician and the OBS.

[Slide.]

I would like to acknowledge the efforts of the FDA review team for this project. In addition to myself, Dr. William Sacks, a radiologist, is the lead clinical reviewer for this PMS. Dr. Sacks has extensive experience in the review of diagnostic devices in the Radiology Branch in our division. You will hear from Dr. Sacks in a few minutes as he presents a summary of the clinical data for this PMA.

Additional clinical input was provided by Dr. Brian Harvey, a gastroenterologist in our branch. Dr. Mariam Provost reviewed the preclinical data and Judy Chen provided a statistical review.

Other members of the review team included: Sharon Miller, who reviewed the safety of the laser used in the device system; Cathy Nutter, who reviewed the device-

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sterilization information; Xuan Vo, who is reviewing the manufacturing information; and Pam Reynolds, who is reviewing the bioresearch monitoring issues with the PMA.

[Slide.]

As previously described by the sponsor in some detail, the device system features three main components; the OBS console, the optical fiber and the system software. The device system is used during endoscopy and, thus, also requires the use of an endoscope.

[Slide.]

The principle of operation for the Optical Biopsy System is as follows: via the optical fiber and working channel of the endoscope, the system transmits low-level light energy to the target tissue or polyp which absorbs the light energy. The source of this energy is a nitrogen-pulsed laser with a wave length of 337 nanometers.

In turn, the tissue releases light energy in a distinguishable pattern also described as a tissue's autofluorescence which is received by the spectrophotometer. As was discussed before, for each polyp that is tested, the operator is instructed to obtain three measurements from three different regions of the polyp.

The software prompts the user to properly place the optical fiber in position and trigger the release of the laser pulse. The final analysis will be conducted only when three complete measurements have been obtained by the system software.

[Slide.]

The concept behind this device is that hyperplastic and adenomatous people release light energy at different intensity and wave-length patterns. In essence, autofluorescence provides a distinguishable fingerprint of the characteristics of the tissue.

The spectral data are received by the spectrophotometer in a series of three excitation frames. The device software interprets the autofluorescence released by the

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tissue by analyzing the characteristics of the spectral data through a statistical model. This model was developed from phase I clinical studies in which the spectral data of hyperplastic and adenomatous polyps were obtained and evaluated.

The software provides a binary decision as to its assessment of the target polyp. The results are displayed to the user as either the display message "suspect" or "not suspect" along with a red or green background.

[Slide.]

To support the safety and effectiveness of the Optical Biopsy System, the sponsor provided preclinical information. With regard to the safety of the laser used in the system, FDA assessed the ultraviolet radiation that was delivered to the target tissue. The total energy density of the laser was calculated to be approximately 318 millijoules per square centimeter.

This level is in order of magnitude below the threshold limit value for chemical substances, physical agents and biological exposure indices as specified by the American Conference of Government Industrial Hygienists. Although this threshold limit is specifically intended to address skin exposure, given our current knowledge base, we believe this is an acceptable limit for mucosal tissue as well.

As a result, based on current existing data, there is no risk of mutagenicity, carcinogenicity or tissue trauma with this device.

[Slide.]

With regard to software documentation, the sponsor complied with the current FDA Guidance on Premarket Submissions for Software Contained in Medical Devices. Based on this guidance, the sponsor determined that the device system has a moderate level of risk.

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Consistent with the guidance, the sponsor provided a description of the software, described the software developmental processes and provided the software requirement specifications and software design specifications.

The sponsor conducted a hazard analysis in the form of a failure-mode effects analysis. In this analysis, each potential component failure is identified. The cause and effect of this failure is assessed. The risk reduction action, in terms of labeling, design change or other, is implemented. And the resultant risk after implementation of this action is evaluated.

Finally, the sponsor conducted a series of verification and validation activities which consisted primarily of emulation/simulation testing, functional testing against functional specifications and random sequence testing.

In summary, the software documentation provided by the sponsor is adequate.

[Slide.]

With regard to device biocompatibility, the only patient-contacting component within the entire system is the optical fiber. This fiber was cleared for marketing under a previous 510(k) application, K973611, for a similar duration and placement of use. As a result, there were no further biocompatibility issues that needed to be resolved within the PMA application.

[Slide.]

With regard to sterilization, the optical fiber is provided sterile and for single use. The fiber is sterilized with 100 percent ethylene oxide to a sterility-assurance level of  $10^{-6}$ . The sterilization method is validated in accordance with ISO 11036 and the EtO residual levels were within the acceptable limits of the 1978 Proposed Rule for maximum residual levels.

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The device system complies with EN 60601 in terms of electrical safety and electromagnetic immunity and emissions.

The mechanical integrity of the optical fiber was evaluated with a friction test, fatigue test, pull-strength test and energy-transmission test. All results demonstrated that the device met the performance characteristics specified by the pass-fail criteria of these tests.

In summary, the sponsor has resolved the issues with regard to the preclinical information on the Optical Biopsy System.

At this point, I would like to introduce Dr. William Sacks who will provide FDA's review of the clinical information submitted in this PMA application.

### **Clinical Analysis**

DR. SACKS: Good morning.

[Slide.]

Broadly speaking, there are two types of diagnostic devices, those that detect and those that discriminate. The OBS, the device we are talking about today, is one that discriminates and, in particular, between the two broad classes of polyps, adenomatous and hyperplastic, for those polyps that are under 1 centimeter that are already detected by the endoscopy.

As a radiologist who has performed maybe 2,000 barium enemas, I was always aware there were two broad types of polyps but I thought they were the ones I saw and ones I missed.

[Slide.]

As we have seen before, the indications for use, and this is just the last portion of it, I want to emphasize one aspect of it and that is that the intended purpose for the OBS is that it increases the sensitivity of the endoscopy examination.

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The sensitivity means, therefore, for concluding that polyps are adenomatous and, therefore, in need of biopsy or, if we are talking about sigmoidoscopy, in need of a recommendation for colonoscopy to follow.

As further stated in the indications for use, this can be achieved with the device when and only when the user regards the polyp as adenomatous if either the device or the endoscopist judges the polyp to be adenomatous. Not all endoscopists base their decision on whether to biopsy a polyp or to recommend colonoscopy to follow sigmoidoscopy on their visual assessment of the polyp type.

Many biopsy every polyp or recommend colonoscopy to follow sigmoidoscopy in the face of any polyp of appropriate size regardless of their visual assessment.

[Slide.]

This represents the data that you have seen before that was gathered in the trial. The first column is the endoscopists alone, on average, across the various centers, based on their visual assessments. Their sensitivity, on average, was 84 percent. Their specificity, on average, was 46 percent.

When they combined their visual assessment with the OBS, the sensitivity went from 84 percent up to 96 percent. The specificity, as was pointed out previously, only dropped slightly from 46 to 43 percent. An important issue here is that the positive predictive value actually went up slightly which just reflects the fact that there was a greater gain in using the device in true positives than there was in false positives. I will be showing you some more of that in a second.

For an endoscopist who biopsies all polyps regardless of their visual assessment, their sensitivity, of course, is naturally 100 percent. There is no way to improve on that. Their specificity, of course, is 0 and, indeed, if they were to use the

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device, their specificity would rise significantly. However, their sensitivity would drop slightly.

[Slide.]

This is a way of showing that same data graphically. The way I have this divided is all adenomatous polyps are represented here on the left, all hyperplastic here on the right, of this vertical line. We have three different situations.

First, for those endoscopists who biopsy all polyps, the box represents that which they would biopsy. You can see that the sensitivity--namely, the proportion of adenomatous polyps which they are biopsying--would be 100 percent. On the other hand, of course, their specificity--namely those hyperplastic polyps that they would not biopsy--would be 0 percent which was the third column in the previous slide.

For those whose unaided visual assessment in the trial would be the basis for deciding whether or not to biopsy or to recommend a colonoscopy, they were found to have an average sensitivity of 84 percent and their specificity was 46 percent. This represents the true positives. This represents the false positives because, again, the box is all positives.

When these endoscopists use their device, and we come to the middle bar, it increased their sensitivity. In other words, the pickup of the adenomatous polyps was raised from 84 percent to 96 percent and, as I pointed out, the specificity dropped only slightly with the false positives rising slightly to reflect the same thing.

The fact that the positive predictive value went up meant that the true positives increased more than the false positives did; in other words, by a greater percentage.

[Slide.]

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This is still another way of presenting the data. For those of you who are not familiar with ROC or relative operative characteristic analysis, just relax; I will walk you through it. This is becoming a very common way of evaluating diagnostic devices because it displays a lot more information in one picture.

What this is is a graph of the true positive rate, or sensitivity--it means exactly the same thing--versus the false positive rate which is 1 minus the specificity. So, as false positives go up, specificity goes down. This end would be 0 specificity, this would be 100 percent specificity.

The data in the trial for the visual assessment of the endoscopists put them at a point right here with a sensitivity of 84 percent and a specificity of 46 percent. What I have here is just the false positive rate, the complement of the 46 percent.

For those who would biopsy every polyp, they would be operating at this point here which would, yes, have a sensitivity of 100 percent but a false positive rate also of 100 percent or, similarly, a specificity of 0.

The data in the trial gave us this result when you combine the device with the endoscopist's visual assessment at a sensitivity of 96 percent, very near the top, and a false-positive rate of 57 percent or, as it was expressed, a specificity of 43 percent.

As you can see from this, if your practice is to base your biopsy decision on your visual assessment, then using the device definitely increases your sensitivity with only a small drop in specificity or, to put it another way, only a small rise in false positives whereas, if you are an endoscopist who tends to biopsy all--and I use biopsy as shorthand for either that or recommended colonoscopy--your sensitivity, this point relative to this, would drop slightly although your specificity would rise quite a bit.

The utility of this kind of a graph is that you can plot as a curve all endoscopists who would have the same discriminatory ability but who might differ in the

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criteria that they use to decide whether or not to biopsy a polyp. Those who would like not to miss any, or miss very few, adenomatous polyps would tend to operate up in this portion. Indeed, in the extreme, those who want to miss none would operate up here.

But those endoscopists who would be willing to miss more adenomatous polyps in order to avoid submitting hyperplastic polyps for biopsy would operate down in this portion of the curve. But, again, this one curve would be a typical presentation of all of those who would have the same discriminatory ability.

Those who had a higher discriminatory ability would be on a curve like here. Again, these are somewhat idealized curves. They are not always this symmetric. They are not always this smooth. But it is almost a certainty, given the data that we have, that the use of the OBS would raise the endoscopists to a higher curve; that is, would increase their ability to discriminate hyperplastic from adenomatous polyps.

Anyone who was perfect, who could always pick out an adenomatous polyp and biopsy it and always could recognize a hyperplastic and never biopsy it, their curve would be just this pair of lines here or they would be operating right up here. That is a perfect test.

Somebody who has no discriminatory ability, the totally useless test would have a curve that would lie along this 45 degree line. So, an ROC curve actually can display a lot of information.

[Slide.]

Despite the company's intended purpose for the OBS, namely an improvement in sensitivity, we may still evaluate the utility of an improvement in specificity for those who biopsy every polyp. So we will ask the panel to discuss that issue.

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One other point, and that is that, as you heard from Dr. Bond, the recommendations are that colonoscopists or endoscopists, in general, do, indeed, be judicious about biopsying polyps and there may be some shift in practice that is coming or even current and we definitely want the panel to weigh in on that particular issue.

One of the problems, as Dr. Wang already referred to, was that there was a departure from the protocol. My figures are slightly different from his. The essence is the same. It depended on, I guess, whether we were talking about under a centimeter, over a centimeter, or whatever. But, in any case, just to summarize that in rough outline, 35 of the 135 patients had at least one polyp that was not analyzed by the OBS, but the investigators. That represents about 26 percent of the patients.

In terms of the polyps that were listed, there were about 279 polyps of which about 94 were not subjected to analysis by the OBS which represents roughly 34 percent of the polyps. So, this question of the protocol departure, while it is true that these were not selected--we accept the fact that these were not selected based on any characteristics of the polyp--and, indeed, you saw from Dr. Wang that this happened because of reasons that had to do with duration of patient sedation or patient comfort and so on.

Nevertheless, it is not necessarily the case that there is no inadvertent bias introduced thereby. We will want the panel to discuss this. Just to give an example, if an endoscopist were to have--if it was their practice to biopsy polyps only on their way out from the cecum to the rectum and they stopped early, it might be that there was a systematic failure to biopsy distal polyps in the sigmoid and rectum and that may have some implications for the case mix.

[Slide.]

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Dr. Way raised the question before about the variation from center to center of the performance of the device. The two slides that Dr. Hawkins showed dealt with the combined sensitivities and the sensitivity of the endoscopist alone. These figures actually show the device-alone sensitivity as it varied from one center to the other.

You can see that there was quite a range, actually. The device-alone sensitivity ranged from 33 percent up to 100 percent. The 33 percent was based on only three polyps and we might just throw that out as an outlier that doesn't have any significance. It could just as easily have been 67 percent.

Nevertheless, even if we do throw that one out, we have a range of device-alone performance of 55 percent to 100 percent.

[Slide.]

That fairly large range could be due to any one of three possible causes or a combination of these. This is just speaking in terms of broad possibilities. First, it could have to do with a difference in performance of the OBS units at the different center. Secondly, it could have to do with the way that the device was used at the different centers and, thirdly, it could have to do with the polyp case mix at the different centers.

The company pointed out that the OBS, and we feel that this is perfectly reasonably, that the first two reasons--that is, the performance of device, itself, and the way it was used probably does not account for that although the discussion at the end there about the fact that two out of three attempts on the same polyp might give a different answer, it is not clear to what extent this might contribute.

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But, even if we assume that it is largely due to case mix, the point is that there was quite a variation and this has a big effect, even though the device is not meant to be used by itself.

[Slide.]

I want to illustrate how that works. Again, back to pictures. If we look at this as the bar on the left being the sensitivity of 60 percent of the endoscopists alone and the bar on the right being on the order of 75 percent of this whole distance being for the device alone, how do we derive the combined sensitivity of the two out of this of 90 percent.

We have to make an assumption in order to do that that the device and the endoscopists have independent judgments; that is, that there is no correlation between these judgments.

First of all, that is reasonable because the endoscopist is basing his or her decision on the morphology and the surface texture and color of the polyp whereas the device bases its judgment, if you will, on the chemical composition of the polyp. There is a no a priori reason that these should be correlated.

That would be reflected in the fact that if the OBS alone picked up 75 percent of the polyps, if there were independence between the two, then it would pick up 75 percent of those that the endoscopists already picked up as well as 75 percent of those that the endoscopists did not pick up.

On that assumption, then, the sensitivity would go from 60 to 90 percent.

[Slide.]

This can be looked at the other way around, same figures, just floating the endoscopist as opposed to the OBS if the OBS picks up 75 percent, the endoscopist picks

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up 60 percent, again, of the ones, the 25 percent, that the device misses, again coming to 90.

So it really doesn't matter which way you look at that. That is useful to keep in mind when you go to ask, "Well, what added information does the device alone have?" That is because of the combining rule that is suggested, namely, again, to remind you, that the polyp is to be regarded as adenomatous if either the endoscopist or the OBS or both regard it as adenomatous. That is what gives this kind of approach.

[Slide.]

Let me show you that not only is that a reasonable assumption that the two are independent, the endoscopist and the device, but the figures that were obtained in the trials actually supports that. The average endoscopist had a sensitivity of 84 percent and the device had, by itself, an average sensitivity of 72 percent.

That would yield, on the assumption of independence, a 96 percent combined sensitivity which is, indeed, the figure that was found in the trial so that this assumption of independence is supported by the data.

[Slide.]

What does this mean in terms of the combined sensitivity with this kind of variability of the OBS alone, sensitivity that we saw went from 55 to 100 percent. If you were to shrink the sensitivity from 75 percent to 50 percent, the effect on the combined sensitivity would be to drop it from 90 percent to 80 percent, even for the same endoscopist with the same 60 percent sensitivity.

[Slide.]

Conversely, if you are talking about a device whose sensitivity is 75 percent or in that center with that particular case mix, and so on, but the endoscopist, instead of having a 60 percent unaided sensitivity had, say, a 28 percent sensitivity, then

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the combined sensitivity would also be pulled down, in this case, just because of the figures I picked, to about 82 percent.

So you can see that regardless of which, whether the endoscopist or the OBS alone has a highly variable sensitivity by itself, the combined sensitivity is very sensitive to each of those as independent inputs.

That raises the question, for example, should this endoscopist, with a visual sensitivity of 28 percent as might be found, say, in those who do sigmoidoscopy who are more and more not gastroenterologists but primary-care physicians, nurse practitioners, physician's assistants and so on who may have very little experience visually distinguishing between adenomatous and hyperplastic polyps, should somebody rely on their own visual assessment plus the use of the device to arrive at a sensitivity of 82 percent rather than just go ahead and operate at that top right corner of the ROC curve; namely, biopsy or send on to colonoscopy for 100 percent of the small polyps.

That is a question we want the panel to discuss.

So that brings us, then, to the questions, the discussion points, that we have presented to the panel. I am just going to walk through these. You have them in your handouts. They are reproduced, hopefully, word-for-word on the screen, but we will go through these together.

[Slide.]

The clinical practice of the colonoscopists enrolled in the pivotal study was to biopsy all polyps based on at least their statement, when asked, "What would you normally do if you were not involved in a trial?" We saw a little bit of that earlier.

That would lead to a sensitivity of close to 100 percent. To quantify the potential benefit of the device, the sponsor computed the sensitivity and specificity of the

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OBS in combination with the visual assessment of the endoscopist and demonstrated a statistically significant improvement when compared to visual assessment alone.

[Slide.]

Part a, what is your understanding first of the current clinical practice with regard to the management of colonic polyps; b, do the data which indicate an improvement in sensitivity from 84 to 96 percent based on the colonoscopists visual assessment support the safety and effectiveness of the device for use by--

[Slide.]

--colonoscopists who do not biopsy all polyps and/or colonoscopists who do currently biopsy all polyps.

[Slide.]

c, do the data support the safety and effectiveness of the device during any lower endoscopy procedure including sigmoidoscopy, during colonoscopy only or any other that you might think of.

[Slide.]

d, do the data which were derived from a diagnostic population also support the safety and effectiveness of the device for use in a screening population of average risk.

[Slide.]

2, the clinical protocol required that all polyps observed during colonoscopy be analyzed by the OBS and by histology. However, in the study population, 35 of the 135 patients had polyps that were not analyzed by the OBS and, therefore, not included in the study. Do these protocol deviations introduce bias that may affect the validity of the sensitivity and specificity calculations?

[Slide.]

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3, the data indicate that the stand-alone sensitivity of the various OBS machines used in the pivotal trial ranged from 33 to 100 percent. The sponsor has attributed this variability to the range of polyp types observed in the different study sites. What effect does this variability have on our ability to accurately compute the expected sensitivity and specificity of the device.

4, labeling is based on the data contained in the PMA. Based on your review of that data, please address the following--

[Slide.]

a, should the indications for use in labeling include all lower GI endoscopy procedures including both colonoscopy and sigmoidoscopy or--

[Slide.]

colonoscopy only in both screening and diagnostic populations or colonoscopy for either population but only when the decision to biopsy is based on visual assessment or any other.

[Slide.]

Or are there additional warnings, precautions or instructions for use that would be appropriate?

[Slide.]

5, if you recommend approval, do you believe that a postapproval study should be mandated as a condition of approval to further evaluate any issues not completely addressed by the data presented in this PMA.

[Slide.]

In particular, what issues should be addressed and, in general terms, what type of study would you recommend?

DR. DONATUCCI: Than you.

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I would now like to ask for any panel members who would have questions of the FDA for clarification purposes to pose their questions.

DR. STEINBACH: Dr. Sacks, did you actually calculate the ROC for OBS alone? Are those just general--

DR. SACKS: There are two parts to that. I didn't even show for the OBS alone and, second, those were just typical curves. We didn't have enough data to actually be able to generate entire curves. We had only the three large points that I had on the curve as data.

DR. WAY: In the calculations of independence between the two, does your conclusion hold up for institutional data as well as combined data, specific institution data. Some seem to be performing a lot better than others, although we don't have all the data.

DR. SACKS: That is a calculation that is independent of what the actual amount, the sizes of those bars, was. All I know is that the averages or the total data that was presented for analysis yielded a result that was consistent with that assumption.

DR. WAY: I think my mental hypothesis is that, in some institutions, the ROC curve might be quite similar without the device than with the device in which case you would look upon the curve for the individual as being the major variable here in the results. The curves for the individual perceptionist, endoscopists.

DR. SACKS: But the increment would still be similar to what was shown. It is true that endoscopists who had a lower sensitivity with less experience would likely not be operating lower on the same ROC curve but would have lower ROC curve.

DR. WAY: It is a different curve.

DR. SACKS: Yes, indeed. But the sensitivity aspect of it would still also be pulled down along with the entire curve as the bar figures that I showed indicate.

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DR. WAY: Then you think that it is excluded that improved criteria in training would eliminate some of the benefit or much of the benefit?

DR. SACKS: No, because even if you were, say, a person who could discriminate 90 percent of the time, if your sensitivity was 90 percent, as I showed, the increments, if you had a device that was right 75 percent of the time, the 10 percent false negatives that you have, that 10 percent that you are missing, it would still pick up three-quarters of those, 75 percent of those.

That is why I showed it either way. You can calculate quickly in your mind what the device would add to that. Obviously, if you have a sensitivity that is 0, then it actually brings you three-quarters of the way up to 100. If your own sensitivity was absolutely nothing, and you used the device alone, you would still get a 75 percent combined sensitivity.

It will always take you three-quarters of the way, if that is the device-alone sensitivity. It will take you three-quarters of the way through your false negatives up to the top. So, no matter where you start, the device will always add its own contribution,

Now, of course, if you were operating in a center where, for some reason, the device's sensitivity is 55 percent, it will only take you 55 percent of the rest of way up. If you have one where it is 33 percent, it will only take you 33 percent of the way up to the top. So you can always sort of quickly, in your mind, just add those two together and see what the combined sensitivity would be based on knowing what either is alone.

DR. WAY: But isn't it true, though, that, at a certain point, a percentage of a small number becomes unimportant.

DR. SACKS: Yes; in that sense. That is for the panel to discuss. That is a clinical issue.

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DR. WOODS: Two questions. One is what percent of the time--this is for the sponsor, actually--what percent of the time did the OBS system predict the normal tissue was normal--not a polyp, but the normal control. Was it 100 percent?

DR. DONATUCCI: Can we hold that question until our discussion?

DR. WOODS: Oh, yes. Okay.

DR. EPSTEIN: I have a question for Mr. Mallis. Could you briefly discuss the calibration of this machine and does it need to be--could there be any potential problems with calibration? Does it need to be periodically recalibrated? Are the internal workings of the machine enough to insure that it works consistently, reproducibly, time after time, and what potential flaws could there be such that the detector might not be working as precisely or as accurately as it should?

MR. MALLIS: In terms of the reliability of the system, that was addressed with the preclinical information that was submitted. So, at a bench level, that should not be an issue. Certainly, as you saw the results, there was some variability between sites. I think we identified that we didn't think the issue of calibration was an issue.

But, certainly, I think that is something that would be more understood when this device is used in more studies or at more sites when calibration has to be done at each site there.

In terms of what is done in each setting, the system is, indeed, calibrated at the start, I guess, by obtaining a normal baseline measurement. That is done prior to the initiation of the actual procedure. Once that is done, the software will review this and, if there is something erroneous that is obtained, it will not allow you to proceed. So that needs to be completed before you can continue so that if, for some reason, if there was

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some miscalibration, it would not allow you to continue with the actual examination with the target polyp in question.

DR. TALAMINI: Dr. Sacks, I appreciate your clear presentation of complicated data. If you could just help me with the error rate of the pathologist and how that would impact on the contribution of the system and upon your analysis of that contribution.

DR. SACKS: When you have an error rate in a gold standard, it is all over the map as to what that does to the sensitivity and specificity of anything that is being prepared for that gold standard. It could actually be higher. It could actually be lower.

We can put limits on those ranges but, the fact is, it is unpredictable what error rates among pathologists will do. We rarely get into that in the FDA. We have to start somewhere and we generally accept as a gold standard the histology.

But, as I say, it could go either way.

DR. TALAMINI: Does that mean that there is a point at which these numbers become meaningless because the gold standard has some error rate or not?

DR. SACKS: I don't think they become meaningless. It is certainly the case that, in centers where you have more experienced pathologists or you have double reading, you certainly get much closer to the gold standard. We just have to start from the basis that that is what you would really need to have to be sure that the device is performing as it is. Other than that, I can't say any more than that.

DR. WAY: But we did hear that the kappa value was 0.9 which is far from perfect and probably in a range that might affect the analysis of the data.

DR. SACKS: I can't tell you, as a radiologist who is always accused of having kappas in the 70 range, how gratifying it is to me to see that the pathologists aren't 100.

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DR. DONATUCCI: Do we have any other questions from the panel?

At this point, we will take a one-hour lunch break before we reassemble and we will reconvene at exactly 12:35. [Whereupon, at 11:35 a.m., the proceedings were recessed to be resumed at 12:35 p.m.]

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## AFTERNOON PROCEEDINGS

[12:35 p.m.]

DR. DONATUCCI: We will reconvene the open committee discussion.

Prior to that, we are going to have Dr. Robert Hawes give us the panel's presentation of this PMA.

### **Panel Discussion**

DR. HAWES: Thank you very much.

[Slide.]

First, as a prelude, my name is Rob Hawes. I would like to state publicly that I have no financial interest in SpectraScience. Also, additionally, I am not conducting nor have I conducted any research in competing technologies or competing companies in the areas of spectroscopy.

I was asked to be the lead reviewer from a clinical standpoint and I have chosen to make some comments sort of in slide form which I hope helps and does not confuse the whole situation.

I will say that I found reviewing this particular technology rather difficult because it has been impossible for me to separate the clinical practice of colonoscopy, flexible sigmoidoscopy and polyp management from a consideration of this technology. But I do want to present some comments which, perhaps for the urologists and the FDA panel, hopefully will be helpful, perhaps will be redundant to the gastroenterologists in the group.

I think that when we review optical biopsy systems as presented, there are two applications which we foresee this being applied to. One is colonoscopy and one is flexible sigmoidoscopy. I think it needs to be stated that these environments--that is,

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colonoscopy and flexible sigmoidoscopy--are completely different environments in a number of different ways.

[Slide.]

Colonoscopy is performed by physicians, primarily by gastroenterologists or surgeons, so it is an examination that takes a considerable amount of skill and is performed by a physician. Also, it is approved for screening but it is reimbursed only in high-risk patients. I think that I will comment a little bit more later.

And then there are many indications besides screening and surveillance so the environment in which you do colonoscopy is not necessarily just for polyp screening.

[Slide.]

Flexible sigmoidoscopy, on the other hand, is increasingly being performed by non-M.D.s. It is clear that if policies that have now been enacted by Congress and the federal government are followed with regards to flexible sigmoidoscopy training, there are probably not enough physicians, in fact, to do all that screening.

So most institutions, many areas, are moving to non-M.D.s performing this examination. I think that will be relevant with further discussion. The indications for flexible sigmoidoscopy are primarily for screening for polyps and polyp detection is really the primary goal.

So it is, in fact, this environment of flexible sigmoidoscopy that I think actually is more apropos to this technology.

[Slide.]

I think another point that is important to put up is that there is, in fact, a disconnect right now between what is being recommended by the National Cancer Institute, et cetera, for colon cancer and colon polyp screening and what is, in fact, being

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reimbursed by payers. In fact, it is the reimbursement issue which is overwhelmingly the strongest influence on our approach to colon cancer screening. People won't do things that they are not paid to do.

[Slide.]

I want also to point out again, not to be redundant or state the obvious, but, again, this technology does not improve our detection of polyps. That actually would be probably a great advance if we could do that, but it does not. Its purpose is to improve the endoscopist's ability to differentiate an adenoma from a nonadenomatous polyp.

[Slide.]

I also think, again, from a clinical perspective that the breakdown, in terms of polyps, is, perhaps, a little bit more--not maybe complex, but at least is more involved than I think what has been presented. I think, again purely from a clinical standpoint, it could be broken down into three different categories.

One are very small polyps, less than 5 millimeters in size. Frequently, these are referred to as diminutive polyps. Those that are greater than 10 millimeters in size are considered sort of advanced polyps. As you heard from John Bond, they are important and cause us to make certain recommendations and so forth with referral to colonoscopy.

This area of 5 to 10 millimeters is sort of intermediate. Again, this will become important I think with further discussion,

[Slide.]

Think, also, for the non-gastroenterologists in the group, we have put forth--in most of the papers, there is this issue of biopsy. But there is a distinction, really, between biopsy and polypectomy. In fact, during colonoscopy, polyps are not biopsied.

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We wouldn't take a 1-centimeter polyp or an 8-millimeter polyp and choose to biopsy it. That is really not the practice of gastroenterology in terms of colonoscopy.

We don't make a decision clinically whether or not to biopsy a polyp. We, actually, in fact, remove them. If the polyp is 1 to 5-millimeters in size, those, generally, can be removed with a single sweep of a biopsy forceps. So cold biopsy forceps are frequently applied to these very small, 2 to 3 or 4-millimeter polyps.

There is also a technology available called hot biopsy forceps. These would be ones in which monopolar current can be delivered to the polyp and the polyp can actually be sort of fulgurated. That is a technique that is frequently applied to polyps in the range of 1 to 8-millimeters.

We also have a technique of cold snare, using a polypectomy snare. This has been described as being a very safe method of removing polyps that are less than 5 millimeters in size. The standard way of removing large polyp is a snare with cautery.

These are the techniques and the technologies that we currently use to remove polyps. Again, I emphasize that we very seldom, if ever, sort of biopsy part of the polyp and then wait around for the pathology to tell us what the histopathology is.

[Slide.]

I think it also needs to be put forth that, at least from an endoscopist's viewpoint and despite what Dr. Bond put forth, is that I think that there is still a very great sense of liability issues that occur with a colonoscopist doing colonoscopy and leaving an adenomatous polyp behind.

It may be that, in the future, this will be an acceptable behavior but I think that we are very reticent as clinicians to knowingly leave behind an adenomatous polyp. The polyp growth rate, we certainly know something about, but there is some question about that.

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The other issue is guaranteed follow up. If you leave an adenomatous polyp behind, you are concerned that that polyp will get follow up in an adequate period of time, at least right now.

And then there are some issues coming out from Japan and other areas of an issue called a flat adenoma; that is, whether or not cancer can actually occur in a very small polyp. That is a hot issue of debate in the United States at this point in time and many people feel that there is a fundamental difference between what is being reported from Asia and what is being reported in the Western World.

But there is still an issue of whether or not some of these small adenomas may be important or not.

[Slide.]

The standard for polyp management during flexible sigmoidoscopy is that if you see a polyp, certainly greater than a centimeter, there is no question that that polyp would be referred for full colonoscopy.

[Slide.]

This is a complex slide. This is a type of algorithm that we would go through if, at the time of flexible sigmoidoscopy, we find a polyp less than a centimeter in size. I have sort of highlighted standards up here because I agree with Dr. Bond that, really, standards are not set in stone.

There is a lot of room for an individual bias by clinicians so there really is not a standard for this and probably, as time goes on, our policies will shift and change. There is certainly a lot of research going on and so that is the reason for the confusion in this slide.

But if, at flexible sigmoidoscopy, a polyp less than a centimeter is seen, there are several options that you have. I would propose that, in the United States right

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now, the great majority of patients are referred straight to colonoscopy. There are a lot of reasons for that, one of which is a very, very strong feeling that colonoscopy, in fact, is a better way to screen for colon cancer and is a better way to go than flexible sigmoidoscopy is to begin with.

So most of us sort of use the finding of a polyp as a reason, a good reason, to refer that patient on to full colonoscopy. I believe that the majority of patients in the United States right now would be referred for full colonoscopy irrespective of the histopathology of the polyp.

But it would be an acceptable strategy in some people's eyes to do a biopsy, whether that is a regular biopsy or an optical biopsy or whatever. If the polyp is found to be hyperplastic, the data is pretty clear now that that doesn't predict significant lesions upstream and many people would full accept redoing a flexible sigmoidoscopy in three to four years.

If, in fact, whatever this biopsy is done, if it is found to be an adenoma, I think, again, there is some consideration. Certainly, right now, most people would be referred on for a full colonoscopy. If these small adenomas are not so important, perhaps, in the future, they will get booted back to flexible sigmoidoscopy, but the standards of what to do with these small adenomas, particularly a single small adenoma is really not known. It is in flux right now and it is difficult to make any standard consideration.

[Slide.]

If you have a diminutive polyp or a small polyp, less than a centimeter, at flexible sigmoidoscopy, one option is just to remove it with cold biopsy forceps. Another one is to do chromoendoscopy. I bring this up just to highlight a point that I think is apropos to our practice.

[Slide.]

at

This involves dye spraying with either methylene blue or indigo carmine. When used with high resolution or a magnification endoscope, you do get some information. When you spray dye on top of a polyp, there are two patterns that can be seen. One is called a pit pattern. This is consistent with a hyperplastic polyp.

The other is a sulci pattern, sort of like the surface of the brain, and tends to be consistent with an adenoma.

[Slide.]

This is a polyp, here on the left, as shown by the endoscopic view. This is post-spray where you see these pits on top of the polyp. This is consistent with a hyperplastic polyp.

[Slide.]

This is the sulci pattern that is seen. As you can see here, it sort of looks like a surface of the brain and this is consistent with an adenomatous polyp.

[Slide.]

I won't go into this data, but a number of institutions have reported results with dye spraying with sensitivities in the low 80s and a negative predictive value of 88 percent. Then, also, looking at distal diminutive polyps, these are very small polyps, the sensitivity and specificity is shown here and negative predictive value.

The main reason that I show that is that, number one, this particular technique is simple and safe. It is compatible with existing endoscopes and you can reuse the spray catheters. It is transportable to most endoscopy units. But, in fact, in the United States it is not used. Virtually no units are doing dye spraying to distinguish between adenomatous and hyperplastic polyps.

So I think that is apropos to the way we are practicing endoscopy.

[Slide.]

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So the options for management, then, would include chromoendoscopy or, as proposed here, is to use spectroscopy, the idea being that the polyp less than 1 centimeter, you do spectroscopy. If it is an adenoma, they get referred to colonoscopy. If it is hyperplastic, they can go on to flexible-sigmoidoscopy screening.

[Slide.]

There are a couple of questions that I have. One is, if small polyps are not important, as Dr. Bond is beginning to feel so, why do we need to distinguish an adenoma from a hyperplastic polyp at all.

[Slide.]

The other thing that I would say, just from a practical standpoint, is if, as an endoscopist, I feel convinced that it is an adenoma that I am dealing with, I think it is unlikely that any device is going to sway my opinion as to what I am going to do. I am going to remove that polyp if it is during colonoscopy.

If the endoscopist thinks that it is hyperplastic but the device shows that it is likely to be adenomatous, then I think that is an environment in which it may change what we do. So I highlight this just to say that I don't think that a device will influence us because of the concerns we have about leaving adenomas behind.

I don't think it is going to influence us if we are convinced that it is an adenoma. If we think it is hyperplastic, then I think it could influence us.

[Slide.]

With regards to safety issues from my own perspective, certainly, the device does appear safe in the hands of experienced endoscopists as was presented today. But I think the one charge we, as a panel, will need to address is what will the safety profile be in non-M.D.s I think, as I alluded to earlier, increasingly, at least in my mind

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as I review this data, the technology seems much more applicable to flexible sigmoidoscopy than it does colonoscopy.

As I said before, increasingly flexible sigmoidoscopy is likely to be done by non-M.D.s I think it is worthwhile to say that most practitioners, even non-M.D.s that are now being trained to do flexible sigmoidoscopy, in general, at least, they are also taught the skill of biopsy. So I think that probably it will be safe in the hands of non-M.D.s

[Slide.]

I think as we contemplate the complication rate--this has been brought up. I certainly have some issues with a colonoscopy complication rate of 3 percent, but the issue of complication rates for a polypectomy, I think, is important. But I think, as a panel, we must remember that, for the purposes at least of this discussion, we have to look at the complication rate for polyp less than 1 centimeter and, perhaps, even for those less than 5 millimeters.

I think that it is the less-than-5-millimeter polyps that I think are most important. Most practitioners, I think, are not willing to leave behind a 6 to 8-millimeter polyp, at least in practice today.

[Slide.]

The other question I had, as I reviewed the data, is, really, the variability across the centers. I was impressed that some centers seem to have very little benefit from the optical biopsy forceps and is it, in fact, possible that only some practitioners will benefit from this device.

Really, if the differentiation of adenoma versus non-adenoma really becomes clinically important, if that becomes really clinically important, the question I have is whether or not visual analysis alone can be improved. I say that only because of

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the variability between centers in the proposal presented here today but also, seen in the data on chromoendoscopy, there was a high amount of variability between centers.

So I wonder if just training us to look at these polyps more carefully may not be an issue.

[Slide.]

I think the important data is in polyps less than 5 millimeters. That is at least my feeling. What is the false-negative rate for the device when the endoscopist thinks the polyp is hyperplastic. Again, this less-than-5-millimeter issue is, I think, important, at least in my view.

The false-negative rate for all polyps less than 10 millimeters is 28 percent but it is this less than 5 millimeters that I am particularly interested in.

[Slide.]

So I think, really, some of the questions that we need to address are when would the technology be applied, colonoscopy or flexible sigmoidoscopy, and, at least in my mind, it seems much more apropos to flexible sigmoidoscopy. Does it, and will it, really have a place in polyp management. And then who should use it, is there an interpretation issue and a technical issue.

So, with that, I am going to stop.

DR. DONATUCCI: Thank you.

Any questions for Dr. Hawes?

DR. TALAMINI: Two questions. Do you have any feel or idea why that dye-spraying method has not caught on in the United States?

DR. HAWES: Because I don't think it has been important up until now whether polyps are adenomatous or not--or adenomatous or hyperplastic.

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DR. TALAMINI: Why would it be important for the Europeans and not us? Are they thinking differently about the issue?

DR. HAWES: Why do you say that it is important for Europeans?

DR. TALAMINI: You said that it was used in Europe but not here in the United States, or did I mishear you?

DR. HAWES: If I said that, I didn't mean it.

DR. TALAMINI: Okay; sorry. The other is is there any data available on the current practice of American gastroenterologists and what percent remove all polyps every time?

DR. HAWES: Dr. Bond may be able to address that better than I. I can't give you a statistic but it is my distinct impression that, at the time of colonoscopy, that colonoscopist endeavor to remove all polyps that are seen.

DR. DONATUCCI: I have a question. The number of polyps that were used to generate the specificity and sensitivity in the dye test was approximately how many?

DR. HAWES: Several hundred.

DR. GIBRIL: One more question. Do we have enough data that suggests that the non-M.D.s who perform flexible sigmoidoscopy have equal efficacy compared with gastroenterologists or M.D.s

DR. HAWES: I think there is reasonable data. Some of it comes from England where non-M.D.s are doing more endoscopy, but some, also, from the United States. Kaiser Permanente, in particular, has been very advanced about getting non-M.D.s to do it.

I think polyp detection rates for people that are adequately trained during flexible sigmoidoscopy are on par with M.D.s doing the procedure.

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DR. WAY: Do you think that there is a role for this particular technology, given the results reported, in the circumstances where we are willing to accept a low level of performance of the endoscopist? In other words, we say, "This person is not measuring up. We are not going to spend the extra time and effort to train the individual. We are not going to try and shift the ROC curve to give it bigger elbow. We are just going to throw this on board as a full-proof method."

DR. HAWES: Again, at least in my view, this applies only to flexible sigmoidoscopy. I certainly hope people who are doing full colonoscopy will have a trained eye at polyp detection. Whether or not that would be applicable to flexible sigmoidoscopy--i.e., you have people trained who can visualize or find polyps which is really the issue with flexible sigmoidoscopy, but not so good at differentiating hyperplastic from adenomatous, I think is probably not important.

I don't think there is a situation where you would have somebody who is particularly poor at polyp recognition who would be doing flexible sigmoidoscopy.

DR. WAY: I am not being cynical about this, but, with the decentralization and the proliferation of those involved in this, isn't that a practical possible consequence, let's say?

DR. HAWES: Again, I think the emphasis for flexible sigmoidoscopy has been in polyp detection. There really has been very little to no emphasis on differentiating hyperplastic from adenomatous polyps. There is certainly great issue with polyp detection. So I think there has been very little effort delivered toward sort of the differentiation between the two.

Now, again, data is emerging. We now know, for instance, that a hyperplastic polyp in the distal colon does not predict significant lesions in the more

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proximal colon. So, to a certain extent, our practice of sort of polyp management, if you will, will be influenced by new data.

I think it is, in part, that kind of data--i.e., the unimportance of hyperplastic polyps in the distal colon--I think is driving the development of this kind of technology. It is emerging that, perhaps, it is important to differentiate the two.

DR. WAY: I asked the question earlier but I would like to ask the same question of you. Is there any way to calculate, based upon any pattern of management that is currently in practice, how this technology could have, in the long run, an effect, a statistical effect, on health.

In other words, we are talking about intermediate objectives like polyp differentiation and that sort of thing in a certain range of polyps. But the big question is in cancer prevention, can that be calculated, because that is, really, it seems to me, what it is all about.

DR. HAWES: I don't know the answer to that question. It is certainly feasible that this technology could have sort of a cost influence--that is, if, really, it can differentiate the hyperplastic polyp and if, indeed, those patients don't need to go on the full colonoscopy, then that, perhaps, can have an influence on things in the long term. But I don't know if I can answer fully that question.

DR. WAY: Just a follow-up question. As I understand it, it doesn't really identify hyperplastic polyps. Its strength is on the sensitivity in identifying adenomatous polyps. So the number of biopsies or removals, excision, is increased.

DR. HAWES: Right.

DR. EPSTEIN: Dr. Hawes, if you had this device in your laboratory today, being an experienced endoscopist, would you use it and how would you use it?

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DR. HAWES: Again, I think, from my perspective, it would only be applicable in my practice to flexible sigmoidoscopy. I, personally, remove all polyps when I see them at colonoscopy. So it would only influence my practice at flexible sigmoidoscopy.

I, personally, and, again, there is not enough data to fully sort of support this, but my own practice is I feel so strongly about colonoscopy as the best method for screening that if I see any polyp at flexible sigmoidoscopy, then I will refer them on to full colonoscopy.

So, in my practice, the way I practice, this would have no influence on my approach to patients with polyps.

DR. EPSTEIN: Based on what you just said, do you feel that flexible sigmoidoscopy has, will continue to have in the future, a significant role in colon-cancer screening?

DR. HAWES: I think that is a really good question. My personal feeling is that, as the cost of colonoscopy is ratcheted down by the federal government, that the cost effectiveness of colonoscopy is going to get better and better. My own personal feeling is that flexible sigmoidoscopy will diminish to an insignificant importance in the next five to ten years. Personal opinion.

DR. GIBRIL: Do you think it adds any benefit in a patient who has single or two polyps on the left side with the flexible sigmoidoscopy by using this device? We are talking about one or two.

DR. HAWES: State that question again; I'm sorry.

DR. GIBRIL: I am saying, you emphasized that you will use this device for flexible sigmoidoscopy more so. If you have a patient who has a single polyp on the left side, or two at most, do you think that this device will benefit using in this case?

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DR. HAWES: There are a couple of data that are not yet presented. One of those is that 40 percent of colon cancers now are outside the reach of flexible sigmoidoscopy. Sometimes, flexible sigmoidoscopy gets only halfway through the sigmoid colon. So, if you follow a strategy of flexible sigmoidoscopy as a screening tool, you are going to miss colon cancers.

A significant number of colon cancers do not have polyps on the left side of the colon. So I think that the best strategy, in my opinion, is full colonoscopy. But, statistically, a finding of a single small polyp in the left colon is not a predictor of a significant polyp on the right side.

DR. GIBRIL: Therefore, you are not going to use the device to help you to differentiate whether it is adenomatous or hyperplastic.

DR. HAWES: I would not. But, again, that is my personal opinion.

DR. GIBRIL: Therefore, you are going to reformulate your emphasis on using the device for those patients who have more than two, to use it on flexible sigmoidoscopy. Is that agreeable?

DR. HAWES: Say it again?

DR. GIBRIL: What I am saying is if you see a single polyp, you are not going to use the device. You are going to remove it.

DR. HAWES: Yes.

DR. GIBRIL: But the device will be helpful if you have more than two polyps; is that right--for the flexible sigmoidoscopy finding, I am talking about.

DR. HAWES: Again, for me, if I see a polyp in the left colon, then I will refer that patient on for full colonoscopy. Again, that is my own personal viewpoint. I think an acceptable strategy, if that patient has a hyperplastic polyp, at least from what we know now, is that it is not a predictor of malignancy on the right side.

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So there is a disconnect here between sort of what I think is an emerging feeling that full colonoscopy is ultimately the best way to go and what statistically is sort of being born out by finding a single polyp in the left colon.

The fact of the matter is that, again, the technology, at least in my mind, is sort of pushing us to think a little bit more about what we do and how we identify polyps. But I think that the policy up until now in the practice of most gastroenterologists is not to make a differentiation between hyperplastic and adenomatous polyps.

Most people, if they want to make that differentiation now, would biopsy it. So they would just take a biopsy of that polyp. They would send it to the pathologist. They would get the result back in a few days time. If it was hyperplastic, then I think most patients now would not be referred on to full colonoscopy. If it was adenomatous, then most would be referred on to full colonoscopy.

DR. EPSTEIN: Dr. Hawes, it is not infrequent that, during flexible sigmoidoscopy or even colonoscopy, we encounter patients, rather than having one single diminutive or small, intermediate, polyp in the left colon but patients that have many, ten, twenty, small lesions. Often, the recommendations are that you biopsy a representative sample of these to determine whether or not they are hyperplastic. But there is not the probability of removing all of those lesions, given the large number and the time involved.

This is, again, not something that is infrequent. Would the device help in those particular cases or what would be your strategy, again, if you had this device available?

DR. HAWES: I think that that is a good point. You have outlined what I think the similar policy is. When we see a number of very small polyps in the left colon,

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small being less than 5 millimeters, the tendency is to biopsy one or two of them with the idea that likely they are hyperplastic.

I think if I had a device available and had a way to identify those polyps in a real-time kind of fashion, that potentially would be an application for it; yes.

DR. STEINBACH: I would like to make a comment on why I do not think that the McNemar test should be used. Whether this should be deferred a few minutes or not is up to the Chairman.

DR. DONATUCCI: You are talking about a statistical test?

DR. STEINBACH: Yes.

DR. DONATUCCI: I think that probably should wait at this point.

Thank you.

We will now begin the open committee discussion with the FDA charges. While this portion of meeting is open to public observation, public attendees may not participate except at the specific request of the panel.

The clinical practice of the colonoscopist enrolled in the pivotal study was to biopsy all polyps leading to sensitivity of 99 to 100 percent. To quantify the potential benefits of the device, the sponsor computed the sensitivity and specificity of the OBS in combination with the visual assessment of the endoscopist and demonstrated a statistically significant improvement when compared to visual assessment alone.

What is your understanding of current clinical practice with regard to the management of colon polyps? Do the data, which indicate an improvement in sensitivity from 84 to 96 percent based on the colonoscopist's visual assessment support the safety and effectiveness of the device for use by colonoscopists who do not biopsy all polyps and colonoscopists who do currently biopsy all polyps?

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Do the data support the safety and effectiveness of the device during any lower GI endoscopy procedure including sigmoidoscopy, colonoscopy only or any other combination or indication? Do the data which were derived from the diagnostic population also support the safety and effectiveness of the device for use in screening population of average risk?

Having read all those, we are now going to go back to them one at a time.

Again, question a is, what is your understanding of current clinical practice with regard to the management of colonic polyps. We will start to my far right.

DR. TALAMINI: As a surgeon, I am not sure I should be the first one to answer this. I don't know any colonoscopists in my sphere of influence that leave polyps behind. It seems to me that they remove any polyp that they see. That was the genesis of my question regarding if there is any data that answers or addresses that question.

There are obvious incentives in that direction. There are financial incentives for taking them out that still remain. We sold the public on the thought that if we remove all the polyps, we can virtually eliminate this disease, so, to wake somebody up after a colonoscopy and say, "By the way, we left a few behind but we think they are okay," that is a hard thing to do.

So I think there are a number of incentives to remove all the polyps. To my knowledge, that is what folks do. So what is of most interest to me, with respect to this device, is whether we are at the beginning or somewhere along an evolution where that practice is going to change to where it is acceptable to leave polyps behind if we are confident they are not dangerous.

DR. DONATUCCI: Dr. Hawes, would you like to add some more to your presentation?

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DR. HAWES: Again, I would agree with that. My opinion is that the balance of endoscopists doing colonoscopy remove all polyps for the reasons that have already been stated. With this concern that, despite the fact that, perhaps, small adenomas may not be significant, that is a quantum leap of faith right now for an endoscopist.

So I think that the overwhelming practice now is to remove polyps when encountered at colonoscopy. Therefore, this technology would not appear to be applicable in colonoscopy.

Now, I think that the environment is different during flexible sigmoidoscopy. In that environment, the clinical management of polyps is different. I think that there is data now to support that, if during flexible sigmoidoscopy, a single or several small polyps are seen and if they are determined to be hyperplastic, that there is sufficient data to not compel one to refer that patient on for colonoscopy.

So, within that environment, this technology, I think, would potentially be applicable.

DR. EPSTEIN: I would like to approach this from a little bit of a different perspective. First off, as a practicing gastroenterology who performs many colonoscopies a month and flexible sigmoidoscopy as well, I don't really consider financial or liability issues. The thing that I consider is the safety of my patient and what the best approach to that individual patient should be in terms of his or her management.

One area where I certainly agree with Dr. Hawes is that if I see a small polyp on sigmoidoscopy, I have a lower threshold for performing a colonoscopy because I know the facts are, very simply put, that 40 percent of cases of colorectal carcinoma occur in the right colon out of the reach of the typical 60-centimeter sigmoidoscope.

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Of course, the variability of reach of the sigmoidoscope is anywhere from the proximal-distal to transverse colon to the mid sigmoid, the depth of insertion having little bearing on how far the scope has actually gone.

In that regard, we tend to have a very low threshold for performing colonoscopy based on that data. Just anecdotally, I have heard some people quip that flexible sigmoidoscopy is equivalent to doing half a mammogram.

Be that as it may, during colonoscopy, the algorithm has changed a little bit, and that is, from a practical standpoint, I do not remove every single polyp the I see. If there are small multiple clear polyps in the distal rectum, and we encounter these where, literally, it is carpeted with these lesions and this is not uncommon, the assumption is that these are hyperplastic in the majority of case.

In the majority, that is true. You are going to miss some adenomas, diminutive adenomas, again, that's true. But most of these patients will re-present for screening within three to five years and be at very low risk. So I think, as most practicing gastroenterologists, we tend to be very pragmatic.

The current practice is to biopsy a representative sample of those lesions, as I mentioned before, and submit them for histopathologic evaluation. Certainly, in those cases, it might be valuable to have some alternative technology available.

The other issue that is quite common is when we see diminutive polyps, it is relatively easy to place a hot biopsy forceps, which is similar to the device that we saw on the screen with the optical fiber, but it is just a biopsy forceps that is connected to an electrothermal unit which, then, fulgurates, or destroys, the tissue.

By and large, whether we are talking here about diminutive polyps or whether we are talking about intermediate polyps or what have you, it would be nice to be able to both identify and treat simultaneously.

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My concern is, in the length of time of the procedure, you have to keep the procedure time down. If you have to place one device and then another device, you have to remove it. There is a fairly lengthy time in removing one device and then inserting another device down the length of 160-centimeter colonoscope to fulgurate or destroy the polyp.

That is a part of the algorithm that was not mentioned here, and that is just in situ polyp destruction of small lesions which is very quick, easy and, in my experience, particularly in the left colon, very, very safe. So that needs to be discussed further and we need to discuss more the algorithm and how these polyps are managed.

DR. DONATUCCI: Ms. Newmann?

MS. NEWMANN: I don't have any comments.

DR. DONATUCCI: Dr. Bennett?

DR. BENNETT: No comments.

DR. STEINBACH: If you could back up one slide, essentially, the last line says, "Statistically significant improvement." I would like to suggest that the McNemar test should not be used. Rather than getting into the arithmetic, I would propose an example, that, instead of using the Optical Biopsy System, there was a nurse standing in the corner, presumably where the patient couldn't see them, and using the statistician's favorite tool, a fair coin.

Whenever an endoscopy negative biopsy was seen, she would flip the coin. If it was heads, the polyp would be considered benign. This method would probably have identified 7 of the 14 positive OBS-negative endoscopy polyps as positive.

If we use the McNemar test, the p-value would be less than 0.05. What I am saying with this is we shouldn't use the McNemar test in this algorithm. Saying that the McNemar test should not be used does not invalidate the argument of Dr. Sacks who

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was looking at independence of the Optical Biopsy System and the endoscopist's evaluation.

Saying what he said a slightly different way, if you look at 41 small polyps that were endoscopy-negative, it has the same sensitivity and actually a little bit better specificity than that that looked at polyps together. But I think that we might not be certain that we have shown statistical certainty that this improves things.

DR. GIBRIL: During colonoscopy, I feel removing all the polyps I see except for the multiple polyps which I might find on the rectum or rectal-sigmoid area. These small polyps, usually the hyperplastic polyps, have a left-sided predominance and, therefore, I try not to waste my time picking all the polyps on that side.

But I won't leave any polyps proximal to that area. This is also important for the surveillance plan because it depends on the number as well as the histology of the polyps you remove. If you have greater than three polyps, although they are small, you might rescope the patient in three years.

Therefore, I don't feel comfortable leaving any polyps proximal to the area I just mentioned. I will be liberal on those on the left side which are very diminutive, less than 5 millimeters, and probably this will be rescoped in five years anyway for screening purposes with flexible sigmoidoscopy and see what happened with those polyps.

DR. WAY: I don't do colonoscopy and I am not certain whether I can, from my own experience and knowledge, say that I understand the full spectrum of practice across the country, but in discussing it this morning, we haven't heard of a philosophy of management that is in common practice that is anything other than relatively aggressive in removing polyps with the exception of Dr. Epstein's comment that one may encounter a special circumstance when faced with ten or fifteen polyps.

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According to my calculations, however, the mean number of polyps in the patients in the study was low, less than 1.5, at least. And there has been no data presented on that particular example so I find that, at the moment, unconvincing to me that it has cited as special usage here.

DR. WOODS: I also am a practicing gastroenterologist and tend to agree with many of the comments that were made by Dr. Epstein. I also am a teacher and train fellows and I am really not aware of any teaching or practice guidelines that would advise not to biopsy a polyp based upon what it looks like as encountered at colonoscopy.

In the practice setting, I don't think you would encounter very many gastroenterologists at colonoscopy that would not biopsy any polyp that they saw. However, the family practitioners and non-gastroenterologists that are doing sigmoidoscopy I think may have a different practice.

I think that we do see them referring those patients that have had polyps identified at endoscopy that they did not biopsy and simply backed out, saw a polyp, and referred them on for colonoscopy.

So, in that clinical scenario, I can see where a device such as this in the sigmoidoscopy setting may be useful. I also want to point out what has been brought up a bit, are these polyps in the rectum that we so frequently encounter that turn out to be hyperplastic. The patient may have ten or twenty of them and, even at colonoscopy, I, myself, don't attempt to remove all of these.

I went through the data that you all prepared for us, separating polyp by location, and it does confirm our clinical perception that most of these polyps are--these hyperplastic polyps are in the sigmoid and rectum.

In fact, of your polyps that were hyperplastic in the study, 48 percent were in the sigmoid and rectum as compared to 17 percent in the cecum and ascending colon.

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So again, I think that goes back to this is where the majority of these polyps are. The majority of these things, if we are just doing flexible sigmoidoscopy, are probably going to be encountered by the nurse practitioners, the family-practice people who are referring the patients in for colonoscopy.

In that setting, as well as in my own setting doing colonoscopy, that might be the time, looking at those specific polyps, that I might use this device and find it useful to me.

DR. DONATUCCI: Dr. Steinbach, do you want to add to your remarks?

DR. STEINBACH: My recollection of reading the protocol is that if a patient was known to have multiple polyps, more than, like, five, he would be excluded and perhaps this could be addressed by the--familial polyposis was excluded, but that was the only thing?

MR. YAGER: Familial polyposis was excluded, but multiple polyps were not.

DR. DONATUCCI: Dr. Hawes, would you like to summarize?

DR. HAWES: I think, in summary, most of us agree that there are two different environments. One is colonoscopy and one is flexible sigmoidoscopy. I interpreted the panel to be fairly much in agreement that the policy for most of us is to remove all visible polyps--this is at colonoscopy--with the exception of multiple diminutive polyps in the distal sigmoid or rectum, in which case, we would tend to sample one of two of them one way or the other and not remove all of them.

Within the environment of flexible sigmoidoscopy, it does appear that the panel agrees that one or two polyps should be sampled and, if they are determined to be hyperplastic, there would be room to not refer on for a full colonoscopy.

DR. DONATUCCI: Thank you.

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Moving on to Question b; do the data which indicate an improvement in sensitivity from 84 to 96 percent, based on the colonoscopist's visual assessment, support the safety and effectiveness of the device for use by colonoscopists who do not biopsy all polyps and colonoscopists who do currently biopsy all polyps.

We will start, again, on my right.

DR. TALAMINI: Yes and no. I think Dr. Sacks was very clear on the second question, you can't improve the sensitivity of 100 percent. Not being a statistician, it seems as if the 84 to 96 percent number, as best as I can tell, is a true one. So, yes and no, I guess.

DR. HAWES: Ditto.

DR. EPSTEIN: I have a little bit of a different take on this question and, particularly, the effectiveness part of it. I don't think there is any doubt about the safety of the device but where I have questions which I think we need to address is the effectiveness.

Particularly, I would be interested in data on the 94 polyps that were not, for one reason or another--more specific information on those--particularly, was there difficulty in placing the probe. Number one, I would like to know if the probe had to be withdrawn to be cleaned of debris or other material.

I would like to know how many times there was failure of the probe to get a reading on an individual polyp because of its location. For you non-endoscopists, polyps can sometimes be notoriously difficult to reach. You get one shot at it. It is a quick shot and that is it. Trying to get something on it three times may be technically difficult.

That raises the issue of the time, the length of the procedure. I would be interested in that aspect; does that increase the length of the procedure? That has a direct

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bearing on patient comfort and safety and sedation, not to mention efficiency and, hence, effectiveness.

So I think we do need to address those issues further. I am not yet certain about the effectiveness part based on that uncertainty that came into the protocol and some of the lack of information that was addressed, or issues that should have been addressed, in the protocol, itself.

DR. DONATUCCI: Would anyone from SpectraScience like to respond now to that?

MR. SIEVERT: You had several questions. The ones I remember, and you can remind which ones I forgot, as far as why certain polyps were not optically biopsied, we had five centers. According to our case-report form, most of these occurred early on while there was the learning curve going on. As people got better, it did not increase the procedure time.

To your point of not having to exchange instruments and getting the analysis in less than a second really, comparatively to biopsy, it actually shortened the procedure.

As far as debris or whatever on the fiber probe having to be withdrawn, there were several cases where the machine did not collect information because of either movement and/or debris. At those times, that particular instrument would be withdrawn, wiped off, reinserted. We are not 100 percent sure which it was, either movement, either improper contact, or debris.

Certainly, there was nothing on the case-report forms that identified foreign objects that were stuck that had to be dislodged.

DR. DONATUCCI: Did that accurately address your questions?

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DR. EPSTEIN: Do you have data on how many times the forceps had to be withdrawn and repositioned and put back in?

MR. SIEVERT: We could calculate that off the case-report form, but we did not do that as part of our analysis.

DR. EPSTEIN: Thank you.

MS. NEWMANN: I think the sensitivity--I agree with yes and no on these questions, but I was wondering did you look at patient tolerability of the procedure? You said it was longer than--as far as safety and effectiveness. Patients like flexible sigmoidoscopy as opposed to colonoscopy--if this is used with flexible sigmoidoscopy, then do they tolerate it? Did you ask any questions afterwards? Is there any quality of this procedure with patients? Did you have data on any of that?

You said the length of time really wasn't that much longer but--

MR. SIEVERT: In lieu of Dr. Wang speaking to only the Mayo experience, I will give you our opinion on the total experience here. There was never an instance where the patient was intolerant of the optical biopsy. It was, essentially, the same as a biopsy where they really could not sense or could not tolerate our part of the procedure.

It was more, especially as you go through the colon, there are certain spots, as the colonoscopists know, that the patient becomes more sensitive. At that point, if the patient remains sensitive throughout the rest of the procedure, at that point, the physician was discontinuing the optical biopsy portion.

DR. WANG: When we did these procedures on these patients, they were sedated. So, really, it is very difficult to assess how tolerable this would be in a flexible sigmoidoscopy because those patients are not sedated. However, the procedure, itself, doesn't really vary from what we clinically do when we do an ordinary biopsy.

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The forceps is identical in much respects to what we use in clinical practice.

MS. NEWMANN: But, in a flexible sigmoidoscopy, they are not sedated.

DR. WANG: Right.

MS. NEWMANN: So if you added this to that, and if, say, this was used for screening, would you have to sedate them, because that does add a big safety issue.

DR. WANG: Right. I would doubt that because the biopsy, itself--if we were saying that we wanted to biopsy that polyp, in the current clinical setting, we would use an instrument very similar to this to do that biopsy.

MS. NEWMANN: In flexible sigmoidoscopies, you don't sedate the patient.

DR. WANG: Right; but we do biopsy polyps even on a flexible sigmoidoscopy and, should we choose to biopsy that polyp on a flexible sigmoidoscopy, we would use an instrument that we have available that looks just like this one.

MS. NEWMANN: But, say, you were a center that was primary care and you were doing flexible sigmoidoscopy and you decided to add this to it, then, going in, utilizing this, would you sedate the patient?

DR. WANG: I would doubt that. I think the amount of time--first off, most of the flexible sigmoidoscopy centers still perform biopsies. The majority of people do. And they don't ever sedate the patients because they are not set up for that kind of monitoring and so forth.

So I don't think they would add that. I would think that using this device would add a little time to the procedure because of just the setup of the optical biopsy unit, the calibration and so forth. But it is not going to add a significant amount of time.

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If nothing else, I have used these devices in patients with Barrett's esophagus. They are kind of intrigued by the lights and buzzing going on. It is kind of more scientific than the endoscopist just saying, "Don't worry about that little bump."

DR. BENNETT: No comments.

DR. STEINBACH: The assumption in this question is that colonoscopists will not change their strategy. I think this is a tool that may change the algorithm. It would not affect b, or part 2, the colonoscopists who currently biopsy and remove all polyps. They are not going to use it.

DR. GIBRIL: I have a similar opinion. But, anyway, if it is considered, I think it is better for those who do not biopsy all polyps because there is a chance of missing the adenomatous polyp.

DR. WAY: My unresolved concerns about efficacy surrounding the variations and performance of the instrument which, to my satisfaction, are not entirely explained, number one, and, secondly, the lack of an argument showing how this will have any effect on health.

DR. DONATUCCI: Before we go on, did you wish to respond to that, those concerns?

DR. BOND: Are we allowed to respond to any or all of these?

DR. DONATUCCI: If you wish to respond to that, you certainly may.

DR. BOND: There have been so many issues. I would like to respond to several. The first is, in the near future, screening, I believe, in this country is going to be done by flexible sigmoidoscopy plus fecal occult blood testing. I think that is absolutely clear. It is going to be another seven or eight or nine years before we have definitive evidence that screening colonoscopy, as Dr. Hawes respectively has promoted. It is something that will be able to be promulgated as a public-health measure.

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There are many, many unanswered questions about screening colonoscopy, not just the timing of it but also whether or not it is safe, whether or not it is cost effective, whether or not patients will comply with that examination as a screening test, all these questions are very important and need to be answered, I believe, before we change from the current recommendations which are solidly based on scientific data.

The reason why most programs recommend a combination of fecal-occult blood testing and sigmoidoscopy is this realization that some 30, maybe 40, percent of cancers in polyps are in the right side of the colon with no distal lesion that would prompt colonoscopy and their discovery if only flexible sigmoidoscopy was performed.

The combination, however, largely corrects the limitations of doing either test, in itself.

The issue of what do we do with these small polyps--I think we have heard, today, the traditional approach to this which is now, I believe, rapidly changing based again on scientific data. The studies show that these are extraordinarily common.

In the National Polyps Study and follow up, 30 to 40 percent of patients at three years were found to have adenomas, these small adenomas, even when the initial clearing examination was considered to be complete. And yet only 3 percent developed advanced adenomas.

Follow-up studies have shown that small adenomas do not predict a higher rate of recurrent metacrinous cancer or even advanced adenomas. I think it has been pointed out that the bottom of the iceberg, costwise, of screening is the need to do surveillance on all of these patients where we find these small polyps.

Then, if we are going to put them under special surveillance, do colonoscopy, it literally is going to price screening way out of the market. This is, really,

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I think, one of the downsides of not embracing a new technology such as this which will allow a streamlining of our approach to these common patients that have small polyps.

As I said, I think that the primary role of this, and I agree with Dr. Hawes, is in flexible sigmoidoscopy, the ability to differentiate real time between an adenoma and a hyperplastic polyp. This has major implications for patients and for compliance with screening that need to be considered in addition to the sensitivity and specificity figures, I believe.

If you can tell a patient, when they come in, have one or two small polyps, that, no, the likelihood that these are not related to cancer but they are hyperplastic, and can tell them right on the spot, I think that this is a major achievement that this optical biopsy forceps would allow us to do approaching the accuracy of pathology.

Now, as far as whether removing all small polyps is really an issue, it should be pointed out that we can't even detect these small polyps very accurately. A study from Dr. Hawes institution where he came from before he went to Charleston at the University of Indiana showed that up to 25 percent of these lesions are missed by experienced colonoscopists.

Yet we know that there is now downside effect of that in the future, as far as we can measure. So I think that we need to focus this discussion on current screening recommendations, how the device is likely to be of benefit, and that is differentiating hyperplastic polyps with no importance from the adenoma that may or may not have importance depending upon its size.

I think that this device, the statistics show very nicely, increases the ability to do that real time approaching the accuracy of pathology.

DR. DONATUCCI: I just want to interject here. To the extent that our time to go through this is all limited, I wish you to respond but I think--in many ways, as

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a urologist, I don't know much about this, but it reminds me of discussions of prostate cancer where it seems we can never agree and we have to agree to disagree in the endoscopy.

So I would like to refocus a little bit of the comments more towards the questions of efficacy about the device that we are talking about right now.

DR. BOND: Let me speak to the efficacy of the visual assessment, if I might, because I think that is what we are comparing, the efficacy of the device plus the visual assessment. I don't think that the endoscopist can differentiate between the adenoma and the small hyperplastic polyp with an accuracy greater than about 60, 70 percent.

It is probably just about a toss up. And yet the ramifications of making that determination are quite substantial. On the one hand, they require a further colonoscopy, may require follow-up surveillance. On the other hand, they require nothing.

So I think that that is a very major determination and probably the cornerstone of the potential role of this device.

DR. WAY: The thing that I don't get from your presentation, John, is that you are talking in terms that the data don't support. You used the phrase, "differentiating by polyps to the extent the pathologists can't." As I see it, the difference between option No. 1 and No. 2 that is on the screen is that there will be more biopsies in category No. 1 and that the negative predictive value is low, that you can't march into the other room and say that the possibility of adenoma has been ruled out.

You have not really distinguished between the various kinds. You are just more sensitive in picking up those that have adenomas. So there are more biopsies being

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done. I don't think you can go in there and dispel this sense of transient anxiety given the statistics. But you can please correct me if I am wrong.

DR. BOND: Remember, we are talking here primarily about screening flexible sigmoidoscopy where the only way to make a determination is to do a biopsy or to make a visual assessment at the present time. If we can increase that visual assessment endoscopist real-time accuracy to approach that of pathology, then, with some errors on the side of the false positives, we are going to greatly improve the decision-making process, so that many patients will not have to be referred for expensive, invasive, potentially harmful, costly procedures such as colonoscopy. The rest accurately can be.

I think that that is, in my opinion, the most important role of this device.

DR. WAY: Let's say that you have a polyp and you say that, "Visually, this is suspicious to me so I am going to biopsy." Then you are in category No. 1 and you have a polyp. It doesn't look suspicious. You use the machine. It says, "Suspicious; biopsy." You have biopsied a polyp you might not have otherwise have biopsied. You have still left some behind that neither the machine nor your visual assessment have singled out for concern, but there are still some false negatives left.

I don't see the circumstance that you described somewhere in the options of patients that I am trying to visualize.

DR. BOND: Remember, the only polyp that would be left behind, without a biopsy, would be one where neither the visual inspection or the optical biopsy forceps, or both, indicated that it was suspicious for an adenoma. If that could be done with a high degree of accuracy, which I think has been shown by the data, it would accomplish a great deal.

DR. DONATUCCI: Thank you.

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DR. WOODS: Before Dr. Bond sits down, I am just a little bit conflicted about one of your statements. You said that the small adenomas don't matter and then you said that size was what was really important. If the small adenomas don't matter, then why do we need to know whether they are adenomas or not by this device?

DR. BOND: I think that is a very good question. I think that the small adenomas probably do not matter. But our practice tends to be so traditional at the present time that we are having difficulty moving into that area, that all of the scientific studies show that it doesn't matter.

If we can have a device that increases the confidence of the endoscopist as to what he or she is dealing with, I think that that would help to move that in that proper direction.

The area of, probably, greatest interest, though, is what Dr. Hawes calls the intermediate-sized polyp. There, it makes a very great difference as to whether the patient needs to be referred or does not need to be referred for colonoscopy. I think it is in that setting, probably, where the device would be most critical.

DR. WOODS: That actually comes to my answer to the question, and you probably don't have the answer to this next one, but the sensitivity of the device--that statistics were calculated based upon all the polyps that were less than 1 centimeter, being improved from 84 percent for the endoscopist to 96 percent with the device.

The intermediate polyps may be more important. I was wondering if you had stratified the data by polyp size and run the same statistics comparing less than 5 millimeters to 5 millimeters to 1 centimeter polyps. My gut feeling, from looking at the data provided for the OBS system alone, is that it is probably more sensitive in the larger polyps.

MR. YAGER: Thank you, Dr. Bond.  
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In your panel pack was included the actual clinical data report. On page 22 of that report, there is a stratification by polyp size indicated there. If you look at that--it should be right in the front of the panel pack, probably one of the first amendments--you will see the stratification of sensitivity for the unassisted endoscopy and OBS-assisted endoscopy by polyp size going from and using the estimation of polyp size given to us by the endoscopist at the time of the polyp being sampled.

That goes from 1 millimeter up to 150 millimeters. If you look at that, at the point of about 3 or 4 millimeters, it is consistently above 90 percent. This is the same data that Dr. Wang presented this morning.

One point I would like to make for Dr. Way as well, and that is quantitatively, in the study, we were able to identify, in the small-polyp category, ten additional adenomas that were not seen by the endoscopist. The price that the combination of the two paid, in terms of additional biopsies, were only two. So, quantitatively, those were the numbers.

DR. WOODS: Would you be able to comment now also on my earlier question of the normal control tissues and the sensitivity of the device with those biopsies?

MR. YAGER: Of the normal tissues identified and categorized, we had one disparate value out of 129 samples.

DR. DONATUCCI: Dr. Hawes, would you like to summarize Question b, and I think our discussion also allows us to summarize Question c simultaneously.

DR. HAWES: I think, again, the discussion suffers, to a certain extent, by this sort of confusion between the practice that we have during colonoscopy and the practice that we have during flexible sigmoidoscopy. I think, as we discussed earlier,

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there seems to be fairly uniform agreement that, at the time of colonoscopy, the overwhelming practice is to remove at least the polyp you see.

So I think my take, if I have a little bit of leeway here, is that the answer, in fact, if this technology is applied to flexible sigmoidoscopy, that if we remove all polyps at the time of flexible sigmoidoscopy, these diminutive polyps, then, if we do not remove all these polyps that the device would be effective.

If there are people who actually try to biopsy off with cold biopsy forceps all polyps during flexible sigmoidoscopy, then, obviously, this technology would have no impact. So I think that the important issue that we are going to have to grapple with is really the difference between our approach to polyp during flexible sigmoidoscopy and those during colonoscopy.

DR. DONATUCCI: Thank you.

Moving on to Question d; do the data which were derived from a diagnostic population also support the safety and effectiveness of the device for the use in a screening population of average risk?

DR. TALAMINI: This seems to be almost the same question because it brings to point the difference between diagnostic and screening endoscopies which is probably the difference between colonoscopy and sigmoidoscopy, largely, so I would defer to your comments about those relative populations.

DR. DONATUCCI: Would you like to add to that, Dr. Hawes?

DR. HAWES: My comment would be that I do think that the safety and effectiveness issues that were, again, derived at colonoscopy and in an diagnostic population likely would be transferrable to a screening population of average risk.

DR. EPSTEIN: I think this is an important question and it is one that remains unanswered by the present study but one that the present study wasn't intended to

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address. Having had the experience of running a national training program for flexible sigmoidoscopy where we train generalists and nurse practitioners and SGNA-certified nurses to perform flexible sigmoidoscopy, I have had a fair amount of experience in the rubicon of general sigmoidoscopy.

I think the question remains unanswered as to whether family physicians and nurse practitioners or anyone in the arena of doing screening flexible sigmoidoscopy is going to have the technical skill and capability to manipulate a biopsy forceps onto a polyp. I think if there are very tiny polyps there, they are going to have a hard time and I think if they see larger polyps that are 8, 9 millimeters, they are going to refer them on no matter what they see.

I think they are going to have a hard time maneuvering the forceps and I question whether they would be using this device. Now this is a different take on what might be occurring in a large university setting where there is direct supervision and training.

But I think, in the general population, we don't know if we gave this device to, from experienced colonoscopists to relatively inexperienced flexible sigmoidoscopists, what would happen at that point. I am uncertain and there is no data. The studies don't specifically support that, so I don't think we can say the answer.

MS. NEWMANN: As a nurse practitioner, I think we could handle the forceps with training. However, I would like to go down another route. Safety; again, I go back to your study. I know you haven't put them under, but my concern is in a primary-care or in that general setting, if you are going to do the flexible sigmoidoscopy under no anesthesia, if you use this, what happens and I am back again to the safety of the patient and then, again, if you have non-physician provider in a primary-care that is not equipped with whatever, what would happen.

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So I feel that there is benefit to this in screening, whether it will be used or not. But I am not sure your study was looking at that, so I am not sure of the safety.

DR. BENNETT: No comments.

DR. STEINBACH: I think, if this device is used in a screening population, we are going to have to change the algorithm. I think it is going to leave more small, hyperplastic polyps and so data collected in the past where all these polyps were removed will not apply.

So it may reduce the time to the next examination.

DR. GIBRIL: I think it is applicable for the screening method, but with the condition that, with the finding of greater than two polyps, only, I believe. If I see only two polyps, I intend not to use it and I think it should not be recommended for that case because there is 4 percent of false-negative values on that.

The patient's future surveillance is based on that flexible sigmoidoscopy whether the patient needs colonoscopy or not. Therefore, I think it should be limited to those with multiple diminutive polyps.

DR. WAY: The efficacy for screening I think involves some kind of value judgment based upon data that are a little bit difficult to get our arms around at the moment. The false-negative rate for the endoscopist's estimate was 30 percent. The false-negative rate for the machine alone was 33 percent.

So 30 percent for the endoscopist's estimate false-negative rate, 33 percent for the device. When the two of them are combined, the false-negative rate is 10 percent. The question is how important is the 10 percent, I guess. So the strategy of biopsying all of them will eliminate that 10 percent.

The question is, if it is important to get the other 20 percent, is it important to get that 10 percent. Since the amount of extra work isn't that much, I think you have to

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come to some kind of decision as to whether it is worth the extra work to call in that extra 10 percent and just biopsy all of it.

So I asked a question instead of giving an answer, but I am still skeptical.

DR. WOODS: I tend to agree with all that has been said and I do think it would be applicable to a screening population of average risk. I do ask the question another way. What about its use in the high-risk patient and I can't help but imagine that patients who are high risk if someone even were to enroll them in the sigmoidoscopy plan, the person who would make the mistake to do that would probably make the mistake to use this device.

So I think we have to be careful about making clear that the indications are followed and clear.

DR. DONATUCCI: Again, would the company wish to respond to any comments? Thank you.

Dr. Hawes, will you summarize, please.

DR. HAWES: I think there hasn't been complete consensus overall, but I think that probably the majority feel that the data generated would be applicable to a screening population but with a couple of dissents or disagreements, one being some uncomfortableness that the study doesn't specifically address the screening population and confounded by the fact that the procedure done to generate this data was, in fact, a colonoscopy which is fundamentally different from a screening flexible sigmoidoscopy.

So I think there is, perhaps, a thin majority that agree with this that is can be transferred but with some concerns because of the disparity between the way that the data was gotten in the study and how it is being transposed to a flexible-sigmoidoscopy screening population.

DR. DONATUCCI: Thank you.

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Moving on the Question 2; the clinical protocol required that all polyps observed during colonoscopy be analyzed by the OBS and by histology. However, in the study population, 35 of the 135 patients had polyps that were not analyzed by the OBS and, therefore, not included in the study. Do these protocol deviations introduce bias that may affect the validity of the sensitivity and specificity calculations?

DR. TALAMINI: I am satisfied that the explanations, both today and in the documents regarding these missing polyps, don't introduce bias affecting the validity of sensitivity and specificity for this particular study. I do think, however, they may raise questions about the device, itself, and how it is used, particularly whether these missing polyps are the same polyps that would have been missed, were unable to be polypectomized or biopsied, or whether there is something unique about the use of the system such that there will be polyps that can't be easily biopsied by the system that can be gotten by other means.

DR. HAWES: I would agree. I think Ken Wang's explanation, and for those of us who do colonoscopy--I think it is understandable when you are dealing with small polyps that there is going to be a wide variety that are difficult to access no matter what you want to do. I don't see any intrinsic trends here that suggest that there was some kind of influence or bias that would be detrimental to the results of the study or the data from the study.

DR. EPSTEIN: I would fundamentally disagree with that. First off, I think if you are involved in a study and you have, as your primary goal, to analyze these polyps, you are talking about 35 out of 135. As an experienced colonoscopist, and this is 94 polyps that were not studied--I think that is a significant number compared to 152 that were analyzed.

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I would be particularly interested in why and what was the specific reason in each individual case as to why they couldn't be analyzed, where the problem lies and what could be done to remedy that. Secondly, I do think that this is a large number of cases and it leads me to grave concern about how well the protocol was followed.

It seems to me to be an excessive number on that regard, and whether or not this would affect the sensitivity of specificity, we can only guess, given the fact that we don't have the data on hand from these lesions.

So I consider that a major deviation from the protocol and I am concerned about it.

MS. NEWMANN: I would like to see more information, too, on why--I think some of what was said was true. It wasn't all in the beginning of the study and I agree that it is a significant number.

DR. BENNETT: I share those concerns.

DR. STEINBACH: My recollection of the data was that 50 of those polyps were in two patients that had a large number of polyps that were not biopsied. Of the patients that had more than one sample, there was a high concordance--it wasn't 100 percent--so that that suggests that the sampling--we are not introducing sampling error by missing some of these polyps.

The other questions of maybe this is warning us about something else, is of possible concern.

DR. GIBRIL: I also express the same concern not only in terms of sensitivity and specificity but also from the standpoint of the device, itself. We could be encountered with multiple polyps in a single patient, in many patients on a day, and what is going to happen with that kind of situation if we rely on this device.

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Therefore, we need to know thoroughly what happened and more information in regard to these polyps which were left out.

DR. WAY: This doesn't concern me as much as I think it does some of the others, but I just wonder whether we can have a little more of a global explanation. It appeared to me that some of the centers were much more committed. I am a little surprised it wasn't possible to generate, for example, far more polyps.

Busy centers are seeing many, many polyps and 172 polyps isn't very many polyps. Some of the centers had only a handful. Whether they were really, truly committed to following the protocol and doing everything you had to do may be part of the explanation for this.

DR. WOODS: I doubt that missing some of the polyps impacted at all on the sensitivity and specificity since a polyp is a polyp and it is going to be one way or the other. But I do share concerns as to why so many were not biopsied. I would just like to have a more official case-by-case explanation as has already been alluded to as to why, perhaps, the device just simply technically doesn't perform well in certain situations.

I would like to be able to understand that.

DR. DONATUCCI: A brief comment by SpectraScience, please.

MR. SIEVERT: You are right. Most of these--it was a large number and, certainly, when you are doing these clinical trials to the company, you never like to see a protocol deviation. It makes you sleep less at night. But it is out of your control and we had to go with the physician's decision not to optically biopsy all polyps as he thought best suited the patient and for the safety of that patient. We just didn't want to argue with that decision.

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We do also agree that most of these missed polyps came from two patients that had a lot of them. So the number looks big, but the number of patients, actually, is very small.

We have also shown that we have had a normal distribution of the polyps we did look at. I think Dr. Woods really hit it on the head for me, actually, and that was the study design was designed that each polyp was its own experiment. Not each patient was an experiment; each polyp.

So, yes, we talked about flexible sigmoidoscopy, colonoscopy and such but, again, I will go back to say that the clinical design was very simple. We were focussed on hyperplastic versus adenomas. A polyp is a polyp. The flexible sigmoidoscopy patient with a polyp is the same patient at colonoscopy with a polyp. So we don't think that the bias was introduced.

DR. NORSTED: A brief comment, please.

DR. DONATUCCI: Okay.

DR. NORSTED: Just again, without getting into a great amount of statistical detail, recall that bias, by its interpretation or definition, means that there was some systematic error introduced into the study by the way in which the polyps were sampled versus a random error; that is, there were just some polyps that may not have been gotten to.

A random error would have just made it more difficult for us to detect a significant improvement by use of the Optical Biopsy System. A bias, if you will, or a systematic error, would have meant that we were intentionally, by the way the protocol was implemented, selectively looking at one type of polyp versus another choosing to ignore one, if you will, that, by its very characteristics, would have produced potentially a different statistical result in terms of sensitivity and specificity.

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Certainly, by the rationales that were provided to us by the physicians in terms of having to come to the end of a procedure due to sedation--that is, the length of the procedure being so long that they maybe had to, then, move on and so forth has given us no indication that there was a predetermined selection of polyps to be ignored, if you will, based upon any characteristics of the polyp, itself.

So we do not believe there is any selection bias, per se, in the type of polyp that were brought into the study.

DR. DONATUCCI: Dr. Hawes, will you summarize.

DR. SCHULTZ: Could I just ask one question? Just for clarification, the point was made earlier about the number of polyps versus the number of patients that were not included in the study. Could you go over those numbers for us one more time because it seems to me that the question came up that it was only one or two patients that didn't have a lot of their polyps biopsied.

I thought the numbers were somewhat higher than that.

MR. YAGER: In terms of the number of patients involved, there were 135 patients that we had a report in terms of total number of polyps present. Of those, 35 showed up as a protocol deviation from the point of view of not all polyps being sampled.

In that population, one patient had 40 polyps in their colon. That was estimated on our case-report form and I will have to say that it was an estimate, too. There was another patient that had at least 8, so there was a wide variety of polyps involved here.

In terms of the total number of polyps not sampled, we heard Dr. Sacks' estimate this morning of the patients and of the polyps that are included in the study. There were 136 patients total, 135 that we had patient polyp information in terms of numbers given to us by the clinicians. Of those, 152 polyps were looked at in the study.

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DR. DONATUCCI: Thank you.

Dr. Hawes, would you like to summarize now, please.

DR. HAWES: It seems like a fairly split decision with about half the group feeling that there is likely no biopsy being introduced because of the fact that not all polyps were sampled and half the group being concerned that, with this high a number, there was some sort of technical reason that certain polyps can't be identified or sampled, or whatever, with this technique.

So I think it is sort of a split decision.

DR. DONATUCCI: The next question has two parts. The data indicate that the stand-alone sensitivity of the various OBS machines used in the pivotal trial ranged from 33 to 100 percent. The sponsor has attributed this variability to the range of polyp types observed at the different study sites. What effect does this variability have on our ability to accurately compute the expected sensitivity and specificity of the device?

DR. TALAMINI: This seems to be the head-scratcher for me. It has been addressed a number of times. It may be an oversimplification, but it seems as if the device worked for some people and not for others. Whether that invalidates some of the sensitivity data, especially since it seems as if the very smaller groups had the lower success rates isn't entirely clear.

So I guess, for me, I would say this raises a question about the data but I am not sure how to interpret the question, especially against the backdrop of a potentially inaccurate gold standard of being off by 5 percent or so.

DR. HAWES: I would exactly match those comments. I think that this was the biggest hooker, sort of, for me, the disparity between the centers. It does seem

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sort of a la Dr. Way's comments that there seemed to be some enthusiastic centers and some not. Some of them were, as stated, 100 percent sensitive and others were quite low.

So I think I would agree. This raises some real concerns about the broad applicability of this technology to a broad spectrum of endoscopists.

DR. EPSTEIN: Actually, I was a little bit less concerned about this. I think, if you look at the overall data, and if you exclude the one center which had a very small number, in any event, I don't think it has a major impact on the study, itself.

MS. NEWMANN: I don't think it is a major issue.

DR. BENNETT: I think the company has explained adequately the reasons for it and I would agree that it shouldn't have a major impact.

DR. STEINBACH: I think, as pointed out, the 33 is somewhat of a red herring. It is more like 60 percent to 100 percent. It may be a warning that there should be more training for the physician.

DR. GIBRIL: I agree with him but, also, I think that 33 percent was a single polyp or something, on one side? I was trying to find out the page, but since that, the number matters how many polyps were studied, therefore, my concern is not that much.

DR. WAY: I have expressed some concern about this. Because, as the machine's function is described, it doesn't leave room for this kind of phenomenon. I don't think we have had it explained, even discounting the 33 percent--why there should be much variation at all is still a puzzle to me.

It suggests that either we are on the borderline with the fundamental technology, itself, the physics, let's say, or that there is more finesse required in the usage of the machine than has been explained, or that maybe the machine, itself, the engineering, is somewhat unpredictable.

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So I think that, of course, you can always explain it on the external environment, in which case it is the polyp type. But we don't have any independent evidence that it is the polyp type. That is just one other option. So I still think this is an unresolved question.

DR. WOODS: I agree with Dr. Way. My biggest concern about this is we are talking about 152 polyps. In the group that had the lowest sensitivity, we are talking about 11 polyps. The center that had the most experience only had 50 polyps.

The point I am trying to make is, in the big scheme of what most of us do on a day-to-day basis, 152 polyps is really not very many. I think my concerns would be that maybe the variations here are simply because the numbers are low.

DR. DONATUCCI: Would the company like to add to--you explained this this morning. Would you like to add anything to that explanation?

DR. HAWKINS: Douglas Hawkins speaking for SpectraScience. There are differences center-to-center. For example, the prevalence, itself, although not statistically not quite significant, did vary quite a bit from one center to another.

To reemphasize that the really large differences were not those seen between the instrument from center to center but between the endoscopists. So it may be that there is a simple explanation in terms of polyp type. Otherwise, it is hard to say what it might be.

DR. DONATUCCI: Dr. Hawes?

DR. HAWES: Again, there seems to be a mixed opinion with some people feeling that, really, the discrepancy is significant. There has been a voice about the small number of overall polyps and then others not voicing much concern and feeling that there is an adequate explanation for a variability.

DR. DONATUCCI: Thank you.

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Moving on to the second No. 3 question, at least in my handout; labeling is based on the data contained in the PMA. Based on a review of that data, please address the following: a, should the indications for use in labeling include, and we will discuss a first, and then b: 1., all lower-GI endoscopy procedures including colonoscopy and sigmoidoscopy or 2., colonoscopy only, in both screening and diagnostic populations or 3., colonoscopy for either population but only when the decision to biopsy is based on visual assessment, or 4., other?

DR. TALAMINI: I guess I would favor No. 1. I have two reasons. One is that it seems as if the future effectiveness of this device would be within a context of a change in the current practice of gastroenterologists moving away from biopsying or removing all polyps to a more selective stance.

If that is the case, I would hate to see a labeling that would potentially limit or impede practitioners from doing that. The second reason is, from a very, very pure point of view, this device is designed to look at a single polyp and say what it is or isn't. From that point of view, it should be applicable to any polyp in the colon.

DR. HAWES: I agree.

DR. EPSTEIN: I, again, think No. 1 would be correct but the data that I would need to see to support that would be in patients having a primary physician performing a sigmoidoscopy, evaluating the polyp by OBSL and then, subsequently, having a colonoscopy with removal of the device and comparing that data.

We don't have that and I also think we heard from Dr. Bond--he said quite clearly that the diminutive polyps are not a problem. The polyps between 5 millimeters and 1 centimeter are an area of clinical study and research and an area that we need to know more about. This is the area being touted for this device.

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So I think it raises the question, based on Dr. Bond's own comments, other than for those diminutive polyps, is this a research tool and, therefore, I think we need more information before we could say that it would be useful in sigmoidoscopy.

MS. NEWMANN: I am going to pass on this one.

DR. BENNETT: I would agree. I think the company has certainly shown that the product is safe. I think the questions of the 151 cases to determine effectiveness is really up to the marketplace if the product is approved to decide if that is enough. So I don't think restrictions on labeling are appropriate.

DR. STEINBACH: The lack of safety with this device would be if we miss a cancer rather than if we perforate the colon. Other than that, sigmoidoscopy seems an appropriate use. Under 4a, part 4, in "other, I would remind the people that the instructions to physicians have four references to off-label uses, whether these references should be in the instructions to physicians handout.

The federal had a big go-around a year ago I think it was drug companies opposed to device companies recommending off-label uses.

DR. DONATUCCI: Do you want to make a response to that, Dr. Bennett.

DR. BENNETT: I am not sure that it is missing a cancer. I think it is missing a polyp, a small polyp, of which 0.25 percent may develop, or will develop, over time into a cancer. So I am not sure that that is the safety issue.

DR. STEINBACH: But, if we give it to 10 million people, that means 200 cancers or something like that.

DR. GIBRIL: Definitely, sigmoidoscopy should be included and I will go for No. 1.

DR. WAY: Same answer.

DR. WOODS: I agree.

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DR. DONATUCCI: Would you summarize that, Dr. Hawes.

DR. HAWES: I am quite happy to summarize this. This seems to be the one issue that we have reasonable consensus on. It sounds like the panel does not feel compelled to limit the application so that it could be applied or labeled for use in either colonoscopy or flexible sigmoidoscopy.

DR. DONATUCCI: Thank you.

Part b of this question is, are there additional warnings, cautions or instructions for use that would be appropriate.

DR. TALAMINI: I might be on shaky ground here but I would proffer that, in the absence of additional data, you might consider saying that a practitioner planning to use this, for his first "x" number of cases, or her first "x" number of cases, 30 or 50, have pathology in addition to biopsy or Optical Biopsy System information because there has been some much variability from center to center so that, for each practitioner, they can figure out if they are using the thing right before they attempted to use it without pathology data.

DR. HAWES: I agree. I think, as I stated earlier, I am a little concerned about the variability and results from center to center. That implies to me, at least, that, although conceptually it seems to be very easy to put the biopsy forceps onto a polyp, which I think all people, hopefully, that are certified to do flexible sigmoidoscopy or colonoscopy can do, that there must be some variable in there.

It is a rather interesting concept to require some sort of correlation with pathology for a certain number of the examinations. I would be in favor of having some verification of training available or mandated, I guess, for this instrument.

DR. EPSTEIN: I would second what Dr. Hawes said.

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MS. NEWMANN: I agree. I think we have to do some training because you are going to have a lot of the practitioners using it. I think that is has to be really laid out.

DR. BENNETT: As one who has been involved in the certification process with just the Urological Society, I see this as a mind-boggling undertaking with a variety of governing bodies including nurse practitioners, physicians assistants, et cetera, that, if certification is going to be given as to how that is going to be given.

So it is not a minor undertaking at all. But I concur with what has been said.

DR. DONATUCCI: I am going to take a moment here as Chair to make a personal remark. I agree. I think we should very carefully consider perhaps making a recommendation in the labeling that the physicians use biopsy correlation. But to mandate, having gone through that, myself, in a postmarket-mandated education situation, it is very, very cumbersome for both the physicians and the company has to meet that requirement.

Thank you.

DR. STEINBACH: I agree with essentially what has been said.

DR. GIBRIL: Me, too. But how about the exclusion of a certain group of patients that they mention, about familial adenomatous polyposis. What about hereditary non-polyposis colorectal-cancer syndrome?

DR. DONATUCCI: You are recommending it in addition of which group, please?

DR. GIBRIL: That should be excluded.

DR. DONATUCCI: An additional exclusion which was--

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DR. GIBRIL: Hereditary nonpolyposis colorectal-cancer syndrome, it was excluded, as a higher group risk because if they base their assessment, their visual assessment, with the OBS and they might miss the 4 percent. I am always going to that 4 percent false negative. You would not take that risk with this high-risk group of patients. So I don't know how to include that, but I think on the labeling it should be put in a way that they should be excluded from this screening.

DR. DONATUCCI: That is your recommended addition to the exclusion. Thank you.

DR. WAY: I agree with Dr. Hawes on this.

DR. WOODS: My only comment was going to be similar to Dr. Gibril's which was that we should make a statement of who this should not be used on, the high-risk patients at high risk for colorectal cancer and polyps probably should have all their lesions removed.

DR. DONATUCCI: Dr. Hawes?

DR. HAWES: It sounds like the consensus is that there should be some exclusions to those people at high risk for colorectal cancer. It does seem that it is a consensus amongst the group that some training needs to be done for all persons who wish to use this instrument.

There has been a pretty strong recommendation from our Chairman and one other that we should not mandate a specific biopsy correlation with the instrument.

DR. WOODS: One comment. I was speaking on the presumption that it would be indicated for use in polyps less than 1 centimeter. I don't know if we need to make a statement, over 1 centimeter.

DR. DONATUCCI: It is already in the labeling.

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DR. TALAMINI: Just a point of clarification. Were you saying that you think a training program would be difficult but that putting in the labeling an instruction that any practitioner should correlate for their first "x" number of cases would be okay or did you feel that both--

DR. DONATUCCI: No, no. I was suggesting that the mandating training--requiring certification--

DR. TALAMINI: Would be difficult.

DR. DONATUCCI: It is difficult and I don't know that we should recommend that. I certainly think that a statement saying that you should correlate with biopsy at first would be fine.

DR. HAWES: Were there any members opposed to that concept of correlating a certain number of cases with pathologic--

DR. DONATUCCI: Making a recommendation?

MS. NEWMANN: How do you track that?

DR. DONATUCCI: You can't. We are speaking, now, of labeling, though. There is a difference between compulsory and recommendation.

MS. NEWMANN: You would recommend it.

DR. DONATUCCI: Correct.

DR. HAWES: Do I need to say anything more?

DR. DONATUCCI: Moving on to question 5; if you recommend approval, do you believe that a postapproval study should be mandated as a condition of approval to further evaluate any issue not completely addressed by the data presented in this PMA? What issues should be addressed and, in general terms, what type of study would you recommend?

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DR. TALAMINI: I would say yes, a study that addresses the primary issues that have been brought up today, that to center variability and really a fairly low number of polyp studied. So I would suggest a study that is considerably larger and that, by virtue of being larger, would remove statistical errors, if you will, from having low numbers in different centers.

DR. HAWES: My own personal view is that this technology is going to be very much influenced by the market. I tend to believe that the market will deal with this appropriately. From a pure science standpoint, I think the things that have bothered people is the environment in which this was done, which is colonoscopy, sedated patients by very well-trained endoscopists and whether that is the accurate distinction between a hyperplastic and an adenomatous polyp can be translated to a flexible sigmoidoscopy environment where non-M.D.s, presumably, will be performing the examination.

So I think I would like to see further study done, more polyps and in a screening flex-sig environment would be my hope.

DR. EPSTEIN: I think we need to see how this device, number one, would perform in flexible sigmoidoscopy in non-sedated patients with non-colonoscopists and, number two, I think we need a little more data on the effectiveness and how efficient you can be at placing this probe.

MS. NEWMANN: I don't have anything. I agree with both of them.

DR. BENNETT: Bob, for a second, I thought that you were not going to recommend a postmarket study. I think that the marketplace will definitely decide what is going to happen with this product if it becomes approved. By the time the postmarketing study is completed, the product will either be very well accepted or not. So I would be against a postmarket study. I think it will occur naturally in amongst the gastroenterologists and whoever else uses it.

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DR. STEINBACH: I think another thing that is naturally going to occur is that this device is expensive enough that when things like this are delivered in our department, the company already sits and holds their hands for a couple of weeks, anyway. So they will be in a position to see this early data, and that the FDA should ask that they pass it on.

DR. GIBRIL: I think further study should be done specifically which includes more diverse physicians, those with less experience as well as the non-physicians who perform flexible sigmoidoscopy. We need to see the performance on that basis.

DR. WAY: I say the same thing in general terms, and that is the company should be asked to support with data the basis for marketing the device. At the moment, I don't think that that has been adequately done. That would mean to do it in the sigmoidoscopy and to do it under screening purposes and get more patients in.

DR. WOODS: I would like to see more information on variability of the endoscopists' expertise with family practitioners, nurse practitioners and even endoscopists, the young versus the older or anyone within that realm. There was enormous variability in this study with experienced people in their ability to predict adenoma versus hyperplastic.

So I agree. I think I would like to see a bit more information, more polyps and more practitioners of various levels of expertise.

DR. DONATUCCI: I think it is important if you are making recommendations for a postmarket approval study that would be as specific as possible at this point in the process because when we start to vote, that is not the time to make recommendations as to what we would require.

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So are there any specific requirements, numbers, et cetera that you could recommend?

DR. WOODS: I don't know about numbers. I would have to plug that into some statistical program. I know the company did that before they started and I saw what the minimum numbers were to achieve significance. But we have to ask someone with more statistical information in their head than me to give numbers.

I would say a study should be stratified based upon the differing groups of people who perform sigmoidoscopy, family practitioners, nurse practitioners and gastroenterologists, number of years out of training, and correlate it with histology again. I predict that the sensitivity of the device is not going to be 96 percent in the hands of non-gastroenterologists and maybe in the hands of some gastroenterologists.

DR. DONATUCCI: My question to you would be probably the sensitivity of the endoscopist in that instance will also not be as it was in this study.

DR. WOODS: That is the whole point.

DR. DONATUCCI: We are talking about postapproval. How would that change, then? What do we do with that data when it comes in?

DR. WOODS: I don't know if I am talking about postapproval or not.

DR. DONATUCCI: That is what the question is here. The question, as it is read, is; if you recommend approval, do you believe a postapproval study should be mandated?

DR. STEINBACH: Of course, you have made an assumption we are all working on and that is that approval has been given.

DR. DONATUCCI: That is the way the question is written.

Bob?

DR. HAWES: I am not sure, Craig, we really addressed this question.

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DR. DONATUCCI: I'm sorry, Bob. I did address you but--one quick comment.

MR. SIEVERT: I just want to make a real quick comment. As we go through this, in talking about the study, I want to remind the panel that we are not asking for approval to have nurse practitioners perform the procedure with the OBS. We have restricted it to the physician.

I would like to point out that, yes, we did have some pretty big endoscopists as part of this study but I think I should also remind the panel that with our clinical studies performed at Mayo, we got a very, very wide range of experience performing the study.

Dr. Wang did not perform all the procedures. We did the procedures at Mayo specifically to get a little bit of a view of how individual expertise may affect the results. I think we have done the statistics on that and Mayo was right in the middle. It was not an outlier on any end.

So I am not saying we have already done it. I am just trying to remind the panel, as you are thinking about some sort of postapproval study, the fact that we are not asking for approval for the nurse practitioner. We are considering this a first step.

We are going to get there. We are going to get into a lot of different areas. It is also why we probably made the error in doing it in colonoscopy when we felt, all along, that its real place was in flexible sigmoidoscopy. That is also why, as part of our labeling, we have included that we think this should be used on small polyps that may warrant further diagnostic evaluation.

In other words, the physician who is removing all polyps is not our market. I can't imagine us going in and trying to make a sale to someone who removes

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them all. We are talking about, in some ways, as part of this discussion, changing clinical practice.

We don't want to do that. I am sure that the agency's intention is not to do that. We know that there is a wide range of how the small polyp is approached. We have talked all day long, now, about the variables in how the small polyp is handled, all the way from doing nothing and visually assessing in the middle to representative, random biopsies to removing everything.

We want to have objective adjunctive information to help decide where it really should be instead of two completely opposite poles. This is an opportunity to do something where we can answer those kinds of questions.

DR. HAWES: I want to go back to what I was going to inquire of you and whether or not we ought to actually go around and discuss this again in the context of the procedure, if it is approved, being approved only for physicians, M.D.s, to do and then, secondly, I think the question wasn't would we like to see a postmarket study, I think, do we mandate that. I am not sure I have a feel for the panel on those two issues.

DR. DONATUCCI: Let's do that. Let's go back again and address these specifically.

DR. SCHULTZ: Could I just make two comments, more in terms of clarification. One is that yes, you can mandate that this device be used by physicians only. What you can't do is you can't discuss, in labeling, anything in regard to board certification or subspecialty training.

So, just to lay out your options, if that becomes an issue, it can either be said that it would be used by health practitioners which would be a more inclusive or physicians only.

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The other issue that I would just like to touch on is the last question did specifically relate to postmarket studies. I think that one thing that needs to be stated is that the panel has a lot of options. Mary is going to go into those options later on. The options include approval with mandated postmarket studies as was questioned and this question specifically related to that.

Obviously, there are questions in terms of the amount of data that is required in order to approve the device. I think that you need to discuss those as separate issues. You need to look at the data that is required to bring the device to market and, if you recommend approval, then what we are asking for is how do you recommend it for approval. That is question No. 4 with regards to labeling.

Furthermore, what additional studies would be necessary if the device were, in fact, recommended for approval. I just want to lay out your options. I am not telling you to do this or to do that, but I just want you to understand what your options are.

If any of those points are unclear, let me know. Thanks.

DR. DONATUCCI: We are going to begin again. Dr. Talamini?

DR. TALAMINI: I need you to repeat my mandate at the moment.

DR. DONATUCCI: The question I think we are discussing is approval with a mandated study, do you believe it is necessary and, if so, which study.

DR. TALAMINI: Just further clarification. Approval with a mandated study, is that an approval contingent upon further study at which time, at the end of that study, approval could be withdrawn or is that it is approved but we want this information and it is approved forever.

DR. SCHULTZ: It is approved with a condition that that study be performed. Until a clear understanding between the agency and the company on what

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that study will look like is forthcoming, the approval would not be forthcoming until we had a clear understanding of the fact that that study would be performed and, in more or less general terms, what that study would look like.

The second part of your question, as I understand it, is assuming, let's say that that study showed results that were unanticipated, what would be the effect of that and the effect could be anything from changing the labeling to accurately reflecting the additional information to changing the indications for use and, in fact, if there were safety issues or there were issues which, in large measure, I would say, altered the effectiveness evaluation, which could, in fact, result in removal of the device from the market, although I would say that that would be somewhat unusual.

DR. TALAMINI: In view of that, I think my opinion would be that, if approved, there would be a postapproval study and that it would address the flexible-sigmoidoscopy screening issue and the numbers issue in that larger numbers would, hopefully, answer the question of center-to-center variability that has come up today.

So my sense would be to ask for a study with larger numbers and in the setting of flexible sigmoidoscopy screening.

DR. HAWES: If this technology is approved for physicians only, I would not recommend a postapproval study.

DR. DONATUCCI: Could you give us the second half of that; if it is recommended for healthcare practitioners, what would you want to see?

DR. HAWES: They are not applying for that, are they? So that would be theoretical. Am I okay, Craig?

DR. DONATUCCI: You are okay. Thank you.

DR. EPSTEIN: I would like to see, if it was recommended for approval, I would be interested in the flexible sigmoidoscopy, the issue of the 5 to 8-millimeter

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polyp and the issue of effectiveness in terms of the operator and the information regarding the patients who are unable to have the probe placed, et cetera.

So I think that study will be combined into one and I think it would be essential that it would be done provided the device was approved.

MS. NEWMANN: If the device is approved, I don't think we should mandate a postapproval study.

DR. BENNETT: As I said before, I concur with that.

DR. STEINBACH: I think the device should be approved and we should mandate the study, that we ask for the data as each instrument is shipped, say the first, I will say, ten polyps from each physician, or each center, for each machine.

DR. GIBRIL: If we approve the device, for example, are we going to get information how this device is being incorporated in--it is approved only for physicians, from what I hear. But how are we going to get information if we approve the device and not have follow up on this? If that is possible, to get information how this device is performing in a variety of different centers, and there result is consistent with what we have seen today, then probably we think it is reasonable.

But I don't understand the logic about a postapproval study when we think what we have seen today is acceptable for using this device.

DR. DONATUCCI: I don't want to usurp your role here, but I think what we are talking about approval but there are certain points in the labeling and recommendations which need further clarification. I think that is primarily what the data from those postmarket studies would be used for.

Am I correct?

DR. SCHULTZ: Again, when you talk about postapproval, you are talking about post a determination of safety and effectiveness. That is number one. That

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gets you to approval. Postapproval, what we are talking about is specific questions that you feel have not been adequately addressed by the current data, that you believe that--again, this is mandated.

The company may say, for their marketing purposes or in order to gain a more expansive label or for whatever reason, that they want to go out and do a postmarket study on their own. That is their business.

What we are looking for from you is a recommendation for or against us saying to them, again, "Until you come to us with a postapproval study that includes the following elements--not completed, but provide us with a plan for a postapproval study that includes the following elements, you do not go to market."

So those are the distinctions. One is that the data is there that shows safety and effectiveness. That gets you approval. And then two types of postapproval studies, one that we mandate and one that is at the discretion of the sponsor.

DR. GIBRIL: I understand now. I think we need more data on flexible sigmoidoscopy for screening.

DR. WAY: Just to repeat my last comment, I really don't feel that the efficacy, the utility of the device, has been supported by the data. We have very few patients. We have some inconsistencies that are not explained. We just learned from a comment made a moment ago that, from the Mayo Clinic, there were variations in the statistics based upon the experience of the individual, or at least an implication of that, that not everybody is Dr. Wang, which means that the ability to change the shape of the ROC curve is known, based upon training, and that will affect the efficacy and all the statistics we have been shown.

So I think that, just based upon the body of data we have now, if it were approved, I think that they ought to iron out this, fill up the basket with the proof that it

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has value under these circumstances. If it is going to be screening sigmoidoscopy, I think that that should be tested.

DR. WOODS: I want to ask another question about postmarketing studies. If we agree that the device, as presented, is effective but we have questions about the efficacy in certain subgroups--for instance, the flexible-sigmoidoscopy or the physician population, is that appropriate for a postmarket study, answering those questions, like, how effective is it in certain subgroups?

DR. SCHULTZ: If you have questions regarding subgroups that are included in the labeling, and what I heard in an earlier discussion was that you are at least considering, at this point, the fairly all-inclusive indication statement. If you have questions about something that is covered in the approval--in other words, that is encompassed within the approval but you feel has not been adequately or completely addressed, that would be an appropriate topic to suggest or to recommend a postapproval study.

If, on the other hand, you were to, say, restrict the label to colonoscopy, then you really could not demand that the company perform a postapproval study looking at flexible sigmoidoscopy. That would be their option if they wanted to add that to their indication, but, at that point, that would go beyond what their approval was.

So I think the answer is, and, hopefully, I am making this clear rather than less clear, but I think the answer is that a mandated, postapproval study, number one, has to be something that is within the label that they are being approved for and that requires further clarification or expansion and, number two, if it is something outside of that, that that would be something that they want to add on their own, that that would be something, again, that they could do but that would not be mandated or recommended to be mandated by the panel and/or mandated by us.

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Is that--

DR. WOODS: I think so. It is totally clear. I think I would echo, then, what has already been said by others about the information they would like to have in postmarket approval studies. In addition, I would like that to be presented more clearly with respect to, in the false-negative group, what the exact fallout of the histology of the polyps that were missed by both the endoscopist and the OBS system was.

DR. HAWES: Once again, I have the distinct pleasure of trying to summarize a wide variety of thoughts. But I think that, again, there appears to be disagreement with about half the group feeling that if this were approved for physicians only, that no postmarket approval were required with the other half feeling uncomfortable, that the environment in which it was tested was not going to be the same environment in which it was actually going to be applied and wishing to mandate that a postmarket approval study be done in the environment of screening flexible sigmoidoscopy with a greater number of polyps involved.

DR. DONATUCCI: Thank you.

At this point, we are going to take a five- to ten-minute break and then reconvene at 3:05.

[Break.]

### **Open Public Hearing**

DR. DONATUCCI: Before we take a vote, does anyone wish to address the panel? Please raise your hand and you may have an opportunity to speak.

Thank you.

### **Panel Deliberations and Vote**

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DR. DONATUCCI: Before entertaining a motion recommending an action on this PMA, Mary will remind the panel of our responsibilities in reviewing today's postmarket approval application and the voting options open to us.

MS. CORNELIUS: Before you make a recommendation, please remember that each PMA has to stand on its own merits. Your recommendation must be supported by the data in the application or by publicly available information. You may not consider information from other PMAs in reaching a decision on this PMA.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical-device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendations must be supported by the safety and effectiveness data in the application or applicable publicly available information. Safety is defined in the Act as the reasonable assurance based on valid scientific evidence that the probable benefits to health, under the conditions of intended use, outweigh any probable risks.

Effectiveness is defined as a reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows: first, approval if there are no conditions attached. Second, approvable with conditions. That panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes or further analysis of existing data. Prior to voting, all the conditions should be discussed by the panel.

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You may also vote nonapprovable. The panel may recommend that the PMA is not approvable if the data do not provide reasonable assurance that the device is safe or if reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

DR. DONATUCCI: We will now consider the panel's report and recommendations concerning P990050 for SpectraScience, Incorporated, Optical Biopsy System required by Section 515, Part C(2) of the Act.

The underlying data supporting a recommendation consists of information and data set forth in the application, itself, the written summaries prepared by the FDA staff, the presentations made to that panel and the discussions held during the panel meeting which are set forth in the transcript.

The recommendation of the panel may be approval, approval with conditions that are to be met by the applicant, or denial of approval.

May I please have a motion.

DR. STEINBACH: I move that the device be approved with conditions.

DR. DONATUCCI: The motion has been made that the device be approved with conditions.

DR. HAWES: Second.

DR. DONATUCCI: The motion has been seconded. Would you please state the conditions that you wish to add to approval.

DR. STEINBACH: The condition of approval is that the company collect data on use in screening sigmoidoscopy as the device enters the market.

DR. DONATUCCI: How many patients do you believe need to be included?

DR. STEINBACH: Ten patients for each machine for the next two years.

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DR. DONATUCCI: At the end of that period, that report would be submitted to the FDA.

DR. STEINBACH: Correct.

DR. DONATUCCI: The motion, as it exists, would be that the device be approved with the condition that a postmarket study be performed, that it include ten patients for each category. We may want to add the categories, specifically, in that it be performed for two years and, at that point, the reports be submitted to the FDA.

Can you be specific about the categories?

DR. STEINBACH: The only category I would have would be sigmoidoscopy.

DR. TALAMINI: Am I allowed to suggest a modification to the condition?

DR. DONATUCCI: Yes.

DR. TALAMINI: Under Roberts Rules, can we do that?

DR. DONATUCCI: You may amend the main motion. Do you wish to amend the main motion?

DR. TALAMINI: I would proffer amending the main motion to allow the FDA to design such a postmarket study along the lines described such that it includes screening colonoscopy and is statistically acceptable.

DR. DONATUCCI: Do I have a second to the amendment?

DR. STEINBACH: I will second that.

DR. DONATUCCI: Anyone wish to discuss this amendment as it stands?

DR. WAY: I would like to speak against the motion. I disagree with approval for the following reasons. I think that the data presented have not satisfied the

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criterion of demonstrating a benefit to health or clinically significant results that would benefit the patients.

I believe the numbers of patients are very small in proportion to what could be gathered and that there is an unknown major variable that has not been explained and that is the training and experience of the endoscopist which is extremely likely to affect the results and any interpretation of the clinical efficacy of the device.

Furthermore, I think that it has demonstrated inconsistency in its performance and I think that the potential value that the panel has been able to postulate for the device is in screening sigmoidoscopy and there has been no data presented in regard to screening sigmoidoscopy or in those who might be performing screening sigmoidoscopy.

Finally, certain members of the panel have postulated that the device might have the greatest value in patients with large numbers of polyps where we find that the participants in the study found that to be the particular circumstance where they wanted to deviate from the protocol and not carry through with the exam.

DR. DONATUCCI: Thank you, Dr. Way.

Any other discussion?

DR. EPSTEIN: I would strongly second what Dr. Way says. I think the numbers in the study are too low. There was too much variability in the sites. Too many patients were not studied. There was no study in the primary target population, which is flexible sigmoidoscopy, which Mr. Sievert, himself, admitted was an error.

We yet do not know what to do with polyps that are 5 to 10 millimeters which Dr. Bond, himself, admitted in his own comments.

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DR. DONATUCCI: Let me interject one thing here. I am not quite sure-- your comments are appropriate, but I think, since we are doing Roberts Rules for the first time, we may be in the wrong spot for these comments.

We will get back to those comments in just a moment. What I would like to do, at the moment, following this flow diagram, which was removed, is that we have had a motion. We are amending that main motion. We have had a second to the amendment. We are discussing the amended motion and then we actually have a vote.

Then there will be time for you to vote yes or no and give your reasons why.

DR. TALAMINI: Wouldn't this be discussion regarding the motion?

DR. DONATUCCI: Oh; okay. Sorry for that. I jumped ahead to the amendment. Is there a spot in Roberts Rules of Order to go backwards? So the motion is off the table.

DR. BENNETT: You are discussing the changes to the amendment is what you are doing. You are still discussing. There have been changes made to the original amendment. They have been seconded and you are now discussing those, which is appropriate.

DR. DONATUCCI: Okay; fine.

DR. BENNETT: Unless no one wants to discuss anymore and then you can vote. But, right now, it seems to me that you are still discussing.

DR. DONATUCCI: I am just trying to follow Roberts Rules here. This is new to me.

MS. NEWMANN: Can I clarify something? Can I ask for discussion on this?

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DR. DONATUCCI: You can. That is a good point, since I was out of sequence, let me let Dr. Epstein finish and then we will go on.

DR. EPSTEIN: I yield the floor back to the Chairman.

DR. DONATUCCI: Thank you.

Now, would you please.

MS. NEWMANN: They are asking for approval for this device in colonoscopy; correct?

DR. DONATUCCI: No.

MS. NEWMANN: For what?

DR. DONATUCCI: For either.

DR. SCHULTZ: Mary, maybe this would be a good time to put up the indication for use statement one more time just so that everybody is clear as far as that is concerned.

DR. TALAMINI: If we are in discussion of a motion, I could add to that discussion of that motion. What is going on in my mind is the differentiation between determining effectiveness of this device to say whether a polyp is adenomatous or hyperplastic versus effectiveness of this device within the context of gastroenterology practice in the United States.

That is where I am having a little bit of trouble in my mind sorting out what our definition of effectiveness is. To some degree, the FDA description helped a little bit but I don't think entirely.

DR. HAWES: I would like to speak against the motion as well and would echo what Dr. Talamini has just said. I think the charge before us is the safety and effectiveness of this machine for the way in which it was described. In fact, the

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algorithms for polyp management are, in my view, irrelevant to whether or not we approve this device.

So I would like to speak against the motion, in fact, feeling that the device should be approved without any postmarket studies because approval is being asked for physicians only performing this, and I think the safety of this device has really not been brought into question in, I think, any of the conversations that we have had.

DR. DONATUCCI: Any further discussion on the motion as it is proposed?

DR. GIBRIL: Can we make an amendment on this? It is approved with conditions.

DR. DONATUCCI: Right now, it is approved with conditions. So let's vote on this motion.

DR. GIBRIL: I want to give more.

DR. BENNETT: Craig, did you ever go to a fraternity? I think the issue of an amendment--it has already been amended, so you have got to allow the FDA to have input. Now, that can be amended, but you have to vote on what is there in order to do another amendment.

DR. DONATUCCI: There is no vote on my flowchart.

DR. BENNETT: So if someone wants to amend what is up there, then I think you need to vote what this is and then you start all over again. And then you can make an amendment.

DR. DONATUCCI: Let's vote.

DR. TALAMINI: But I think that we would clarify that if we vote nay here, there can be another motion.

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DR. DONATUCCI: Let's register votes on the motion, approved with conditions as the conditions are stated there.

DR. TALAMINI: No.

DR. HAWES: No.

DR. EPSTEIN: No.

DR. STEINBACH: Yes.

DR. GIBRIL: Amendment can be done now?

DR. DONATUCCI: No.

DR. GIBRIL: Yes.

DR. WAY: No.

DR. WOODS: No.

DR. DONATUCCI: The current motion has been disapproved. Now, is anyone going to make a motion to reintroduce--please.

DR. HAWES: I would like to move to approve this device for use by physicians with the condition that it not be applied to patients with familial polyposis and that no postmarket approval study be mandated.

DR. STEINBACH: I will second the motion.

DR. DONATUCCI: The motion has been seconded. Any discussion?

DR. TALAMINI: I have a point of discussion. Do these votes include the labeling--the labeling would be as stated in the application and not the modifications that we discussed with this question. Is that correct?

DR. DONATUCCI: Correct.

DR. TALAMINI: So if we wanted an altering in the labeling, that would need to be part of a motion; is that correct?

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DR. HAWES: That was part of my motion, to put the caveat of not applying to patients with familial polyposis.

DR. DONATUCCI: The motion is, as we see, approval for use by physicians not applied to patients with familial polyposis, no postmarket study.

DR. TALAMINI: I would like to propose an amendment to the motion.

DR. DONATUCCI: First, we are just going to discuss this. Any other discussion?

Would you like to amend now?

DR. TALAMINI: I would propose an amendment that FDA determine a number of cases, that the labeling include a statement that the practitioner have a certain number of cases, to be determined by the FDA, wherein the practitioner obtains biopsy material to confirm their analysis by the system.

DR. HAWES: Second.

DR. DONATUCCI: Discussion of this proposed amendment to the main motion?

As there is no discussion, we will take a vote. The current motion is approval for use by physicians, not applied to patients with familial polyposis, no postmarket study, that labeling include recommendation of a certain number of biopsies to be performed to correlate with pathology.

Discussion of this motion?

Since there is no discussion, can we have a vote on this motion?

DR. WAY: Don't we have to vote on the amendment to the motion first?

DR. DONATUCCI: Correct. Vote on the amendment.

DR. TALAMINI: So this is an amendment vote now?

DR. DONATUCCI: We are including, now, labeling.

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DR. TALAMINI: I vote yes.

DR. HAWES: Yes.

DR. EPSTEIN: No.

DR. STEINBACH: Yes.

DR. GIBRIL: No.

DR. WAY: No.

DR. WOODS: No.

DR. DONATUCCI: That went a little bit too quick.

DR. TALAMINI: Talamini is yes.

DR. HAWES: Hawes is yes.

DR. EPSTEIN: Epstein, no.

DR. STEINBACH: Steinbach, yes.

DR. GIBRIL: I said no.

DR. WAY: Way, no.

DR. WOODS: Woods, no.

DR. DONATUCCI: Right now, the no's are four and the yeas are three.

That was a vote on the labeling addition to the motion. So the motion now goes back to as it was without the labeling, does it not?

Now, the motion, as it stands, is approval for use by physicians, not applied to patients with familial polyposis, no postmarket study.

We have already discussed, so we will have a vote on the motion as it stands right now.

DR. TALAMINI: Yes.

DR. HAWES: Yes.

DR. EPSTEIN: No.

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DR. STEINBACH: No.

DR. GIBRIL: No.

DR. WAY: No.

DR. WOODS: No.

DR. DONATUCCI: The votes are five no, two yes.

DR. WAY: I would like to make a motion.

DR. DONATUCCI: Please make a motion.

DR. WAY: I recommend disapproval.

DR. DONATUCCI: The motion has been that the PMA be disapproved.

Is there a second?

[Second.]

DR. DONATUCCI: The motion has been seconded. Discussion of this motion?

Then, we will have a vote.

DR. TALAMINI: My only point of discussion is doesn't rejection of the last motion effectively disapprove? Or am I missing something?

DR. DONATUCCI: No; it does not.

DR. DONATUCCI: We will have a vote again, please.

DR. TALAMINI: No.

DR. HAWES: No.

DR. EPSTEIN: Yes.

DR. STEINBACH: No.

DR. GIBRIL: No.

DR. WAY: Yes.

DR. WOODS: Yes.

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DR. DONATUCCI: The nos are four, the yeas are three, so this motion is disapproved. Do I have another motion? We have had approval with a specific condition that was voted down. We have had approval with additional conditions that were voted down. We have had blanket disapproval which has been voted now.

So we have two choices, it seems; approval or approval with a different set of conditions. Would someone like to introduce a new motion?

DR. BENNETT: Go through that disapproval again. You are voting to disapprove.

DR. WAY: Can I ask a question. I was the one who made the motion. As I understand it, if we disapprove, it would give the company an opportunity to come back with more information and argue its case again. It is not a final action at all. I just feel, and the purpose of my motion in the first place, was I didn't think the data supported the proposal but I did not imply that I didn't think the data could not be obtained that would support the proposal.

DR. DONATUCCI: Again, we have a motion for disapproval. I am going to read the votes that I recorded, and you correct me if I am wrong. Dr. Talamini, you voted no towards disapproval.

DR. TALAMINI: Correct.

DR. DONATUCCI: Dr. Hawes, you voted no towards disapproval.

DR. HAWES: Correct.

DR. DONATUCCI: Dr. Epstein, you voted yes for disapproval.

DR. EPSTEIN: Correct.

DR. DONATUCCI: Dr. Steinbach, you voted no for disapproval.

DR. STEINBACH: Correct.

DR. DONATUCCI: Dr. Gibril, you voted no for disapproval.

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DR. GIBRIL: Correct.

DR. DONATUCCI: Dr. Way, you voted yes for disapproval.

DR. WAY: Yes.

DR. DONATUCCI: Dr. Woods, you voted yes for dis approval.

DR. WOODS: Yes.

DR. HAWES: I would like to make a motion to approve with conditions, that the condition mandate a postmarket study using this technology in a screening flexible-sigmoidoscopy study with an appropriate number of cases in polyps determined by statistical analysis to determine the efficacy of this device in distinguishing hyperplastic from adenomatous polyps, so essentially approval with a mandated postmarket--

DR. DONATUCCI: I will read it. The current motion is approval with a condition, the condition being postmarket study screening flexible sigmoidoscopy with an appropriate number of patients determined by statistical analysis.

Do I have a second?

DR. STEINBACH: I will second that?

DR. DONATUCCI: This condition is open for discussion.

DR. WAY: I have a question. I have a philosophical problem here. We are asking for a postmarket study to determine the efficacy. It seems to me that the condition for voting for approval is efficacy.

DR. DONATUCCI: Any other comments?

DR. EPSTEIN: I would just like to second those comments and restate what I said initially.

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DR. HAWES: For further discussion, I think the efficacy has been adequately determined in the environment of colonoscopy performed by physicians. The company is requesting approval for the device to be used by physicians.

The only question is, really, what environment the efficacy needs to be shown. The reason for my motion was that the environment of screening flexible sigmoidoscopy seems to be a hang up for the group, that the efficacy was proven in the environment of colonoscopy and the question is whether or not it will hold true, or hold up, with larger numbers in the environment of screening flexible sigmoidoscopy.

Again, I would reiterate to the group that the approval of this device, to my mind, has nothing to do with our management of polyps. There are certainly a lot of questions out there about the management algorithm for polyps.

The question at hand, and the one that we need to vote on as a committee, is whether or not this can determine safely, can it be used safely, number one and, number two, whether it can aid the endoscopist in determining whether a polyp is adenomatous or hyperplastic, not whether this is going to be used, when it is used, how it is used, in the overall algorithm of polyps.

That is a basis for my motion.

DR. EPSTEIN: Point of order or discussion. I think that our concern is that the study, itself, may be seriously flawed in that the large number of patients that were not included, the number of polyps that were not studied, the variability in the study sites, the open questions that are there.

I think that additional data and additional study needs to be done to confirm that. I think that is our major areas of concern.

DR. WOODS: I echo what Dr. Epstein says and I think my major concern is the small number of patients being studied by expert, or mostly expert, endoscopists

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and the efficacy, I suspect, is going to be not 98 or 96 percent in the hands of the M.D.s who are not colonoscopists using this device.

I would like to see more numbers and I would like to see the false-negative polyps again stratified more carefully to see what the true missed rate is going to be of high-risk polyps, the villous adenomas, the carcinoma in situ. It is probably going to be low, but 10 percent is still important.

14 percent of a missed rate, or 5 percent of a missed rate, is still important if the histology on those polyps is important histology. I think we need to see a thousand patients or several thousand patients with data on them before we can say that what we see in 152 patients is applicable to all polyps that we encounter at flexible sigmoidoscopy.

DR. DONATUCCI: Any other comments?

Now we are going to vote on this motion, this amendment to the approval with condition.

May I have a vote, please?

DR. TALAMINI: Talamini, yes.

DR. HAWES: Hawes, yes.

DR. EPSTEIN: Epstein, no.

DR. STEINBACH: Steinbach, yes.

DR. GIBRIL: Gibril, yes.

DR. WAY: No.

DR. WOODS: No.

DR. DONATUCCI: It is yes, four, no, three, to this motion.

DR. HAWES: Once we get a majority, is that the endpoint?

DR. DONATUCCI: Yes.

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DR. HAWES: Move to adjourn.

[Many seconds.]

DR. DONATUCCI: We are adjourned.

[Whereupon, at 3:35 p.m., the meeting was adjourned.]

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