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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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November 18, 2008
8:30 a.m.

Marriott Gaithersburg Washingtonian Center
Salons C and D
9751 Washingtonian Boulevard
Gaithersburg, Maryland

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JOSEPH LoCICERO, III, M.D.	Chairperson
MICHAEL OLDING, M.D.	Voting Member
REBECCA ANDERSON, Ph.D.	Consultant
MICHAEL BIGBY, M.D.	Consultant
KAREN BURKE, M.D., Ph.D.	Consultant
TED GOOLEY, Ph.D.	Consultant
STEPHEN LI, Ph.D.	Consultant
MARY McGRATH, M.D.	Consultant
AMY NEWBURGER, M.D.	Consultant
ERIN WALKER, M.D.	Consultant
MICHAEL HALPIN	Industry Representative
KAREN RUE, R.N., M.B.A.	Consumer Representative
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PUBLIC SPEAKERS:

KELLEY REDBORD, M.D., American Academy of Dermatology

J. CHRISTOPHER MARMO, Allergan Medical

ALAN H. GOLD, M.D., American Society for Aesthetic Plastic Surgery

RICHARD D'AMICO, M.D., American Society of Plastic Surgeons

ARNOLD WILLIAM KLEIN, M.D., UCLA

ANDREA PUSIC, M.D., American Society of Plastic Surgeons

IRA LAWRENCE, M.D., Medicis Pharmaceutical Corporation

ROBERT WEISS, M.D., American Society for Dermatologic Surgery

STEVEN FAGIEN, M.D., Allergan Medical

DIANA ZUCKERMAN, Ph.D., National Research Center for Women & Families

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M E E T I N G

(8:30 a.m.)

DR. LoCICERO: I want to call this meeting of the General and Plastic Surgery Devices Panel to order. I'm Dr. Joseph LoCicero. I'm the Chairperson of this Panel. I am a thoracic surgeon by trade, and I'm currently the Director of Surgical Oncology at Maimonides Medical Center in Brooklyn, New York.

As a reminder, if you haven't already done so, please sign the attendance sheets that are on the tables by the doors.

Dr. Lim, the Executive Secretary of the General and Plastic Surgery Devices Panel, will make some introductory remarks.

DR. LIM: Good morning, everyone. Can you hear me?

UNIDENTIFIED SPEAKER: Yes.

DR. LIM: I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the General and Plastic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants

of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with the federal ethics and conflict of interest law covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meetings, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

For today's agenda, the Panel will receive an update on safety information collected on dermal fillers in the commercial setting, discuss current premarket and postmarket approved study designs, and make recommendations on general issues concerning the study of various dermal fillers. In addition, the Panel will discuss the design of clinical trials for future premarket submissions seeking approval of dermal fillers for new intended uses.

This is a particular matters meeting of general applicability.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has

been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act to Dr. Michael Olding. Dr. Olding's waiver addresses a stockholding with a firm at issue. He received from $25,001 to $50,000 for this involvement. This waiver allows Dr. Olding to participate fully in today deliberations. FDA's reasons for issuing the waiver are described in the waiver documents which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htlm.

Michael Halpin is serving as the Industry Representative acting on behalf of all related industry and is employed by Genzyme Corporation.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

Before turning the meeting back over to Dr. LoCicero, I would like to make a few general

announcements.

Transcripts of today's meeting will be available from the Free State Court Reporting. Brochures are on the table outside the meeting room.

Information on purchasing videos of today's meeting can also be found on the table outside the meeting room.

I'd like to remind everyone that members of the public and press are not permitted around the Panel area, which is the area beyond the speaker's podium.

The press contact for today's meeting is Siobhan DeLancey. Siobhan, will you please stand? Thank you.

I request that the reporters wait to speak to FDA officials until after the Panel meeting has concluded.

If you're presenting in the open public hearing session today and have not previously provided an electronic copy of your slide presentation to us, please bring your slide presentation to the AV table.

Finally, please silence your cell phones.

Thank you very much. Dr. LoCicero.

DR. LoCICERO: Good morning again. At this

meeting, the Panel will discuss general issues concerning various dermal fillers. The morning session will focus on postmarket information and the afternoon session will involve study design issues.

Before we begin, I'd like to ask the Panel members and the FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position and your affiliation. I'd like to begin to my right and go around counterclockwise.

DR. NEWBURGER: I'm Dr. Amy Newburger. I'm a dermatologist in private practice in Scarsdale, New York. I teach as an attending at St. Luke's Roosevelt Hospital Medical Center where we have a dermatology residency training program.

DR. GOOLEY: My name is Ted Gooley, and I'm a biostatistician from the Fred Hutchinson Cancer Research Center as well as an affiliate professor in the Department of Biostatistics at University of Washington in Seattle.

DR. LI: Dr. Steve Li. My area of expertise is in materials and engineering, design and medical implants. I'm the President of Medical Device Testing and Innovations in Sarasota, Florida.

DR. WALKER: My name is Dr. Erin Walker.

I'm in clinical practice in dermatology in White Plains, New York.

MS. RUE: I'm Karen Rue with Griswold Special Care. I'm the Consumer Representative from Lafayette, Louisiana.

MR. HALPIN: I'm Michael Halpin. I'm the Industry Rep. I'm the Vice President of Regulatory Affairs with Genzyme Corporation which manufactures and develops dermal fillers as well as other products.

MR. MELKERSON: I'm Mark Melkerson, the Director of the Division of General, Restorative and Neurological Devices.

DR. ANDERSON: I'm Dr. Rebecca Anderson. My expertise is in quality of life outcomes and ethics. I'm a psychologist and professor in the Department of Surgery, Epidemiology and Psychiatry in Behavioral Medicine at the Medical College of Wisconsin.

DR. BURKE: I am Dr. Karen Burke. I have a private dermatology practice in New York City, and I'm associated with the Department of Dermatology at Mt. Sinai Medical Center. I teach residents and do basic research.

DR. BIGBY: I'm Dr. Michael Bigby,

Associate Professor of Dermatology at Harvard Medical School and Beth Israel Deaconess Medical Center. My interests are in evidence-based dermatology and immunology.

DR. McGRATH: I'm Mary McGrath. I'm a Professor of Surgery at the University of California, San Francisco. I'm a plastic surgeon in clinical practice and all of the other academic pursuits.

DR. OLDING: Michael Olding. I'm Chief of Plastic Surgery at George Washington University here in Washington, D.C.

DR. LoCICERO: We'll now proceed with the open public hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, to present data, information or views relevant to the meeting agenda.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of any individual making the presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement,

to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of the meeting.

For example, this financial information may include a company's or a group's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

As we have a number of speakers today, I'd like to go over the process to ensure a smooth transition from on speaker to another. AnnMarie Williams will direct you to the podium. When you begin to speak, the green light will appear. A yellow light will appear when you have one minute remaining, and at the end of 10 minutes, the red light will appear and your presentation should be concluded. Since we have a number of speakers, it is very important to adhere to the 10 minutes, and we're going to be ruthless on that.

The Panel will be given an opportunity to

ask questions of the public presenters at the conclusion of the open hearing. If recognized by a Panel member, please approach the podium to answer questions.

I would like to remind the public observers at this meeting that public attendees may not participate except at the specific request of the Chair.

The first speaker will be Dr. Kelley Redbord. Dr. Redbord, please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

DR. KELLEY REDBORD: Good morning, and thank you. My name is Kelley Redbord. I'm a board-certified dermatologist here in town. I work in Vienna, Virginia, in private practice. I'm a member of the American Academy of Dermatology, which I represent here today, and I'm also a member of the Academy's ad hoc task force on patient safety and quality.

I would like to thank the Panel for the opportunity to share the views of the American Academy of Dermatology on the issue of dermal fillers.

I do not have any conflicts of interest in -- or financial interest.

With the growing demand and appreciation for dermal filler products and cosmetic devices, especially establishing sound pre and postmarket study protocols is critically important. We are pleased to see that this is being discussed by the Panel.

The Academy would like to emphasize that in addition to the IBS cosmetic applications of these products, they are also very important for the treatment of scarring and damage from medical conditions and trauma and for correcting facial asymmetries with results from congenital, accidental or medical causes. Above all, ensuring that the products are safe and effective is critically important.

The Academy urges the Panel to consider the level of training and supervision of the individuals administering dermal fillers, as well as appropriate patient selection.

Many complications can be prevented by implementing systems to ensure that professional injecting fillers have undergone appropriate training and use of the fillers and are adequately supervised.

The background materials state that the narrative from a number of adverse events reports implies that the injections of dermal fillers were performed by untrained personnel in settings other than health clinics or doctors' offices.

In the summary of the postmarket data, however, there is no discussion about the level of training and use of the fillers or the presence of supervision of non-physicians for the 930 adverse events.

The Academy would urge consideration of these variables in future studies to determine the relationship, if any, between level of training and rate severity of complications with these products.

I am a co-author along with the American Academy of Dermatology President, Dr. Bill Hanke, on a number of studies on polylactic acid or Sculptra. Two previously published studies evaluated lipoatrophy in the HIV patients and also in patients with normal immunity and lipoatrophy at aging. We reported the incidence of complications is extremely low when proper technique and properly trained people are administering these products, including proper dilution, proper mixing, the proper technique of injecting and injecting into the subcutaneous fat.

A third study has recently been accepted and will appear next month in the Journal of American Academy of Dermatology, addresses the issue of early versus long-term complications.

These studies looking at long-term effects are critical to fully assessing the risk protocol for these products, and the Academy supports this type of research.

The Academy of Dermatology also has a number of initiatives which aim to improve patient safety broadly, which apply to this discussion. Accuracy and thoroughness of data collected on adverse events is critical to evaluating the safety of all drugs and devices. The Academy is working to promote reporting and educating its members on how to report adverse events.

In addition, we are launching a web-based dermatology lexicon called Dermlex. In dermatology, the accurate interpretation of a single word in a patient's history can be critically important. Dermlex codifies and thereby attempts to bring consistency to the use of common dermatological terminology including diagnoses, their synonyms, morphological terminology with textual and illustrated definitions, therapies, procedures and

lab tests.

Finally, the Academy believes there is great opportunity for collaboration among the various stakeholder specialties to build consensus around criteria for evaluating the safety and efficacy of procedures and devices such as those being discussed today.

We have already met and discussed with the ASPS, the American Society of Plastic Surgery, the idea of partnering to convene a consensus conference. While we would invite other organizations, we believe as the primary users of dermal fillers in patient care, it is appropriate for us to lead this collaborative effort.

Thank you again for the opportunity to comment on this issue. We hope that the FDA will consider the Academy as a resource. Thank you.

DR. LoCICERO: Thank you, Dr. Redbord.

Next will be Dr. Richard D'Amico.

DR. D'AMICO: Dr. LoCicero, my apologies. My remarks are actually outside the room being edited right now, and I wonder if I could beg the indulgence of the Panel to either switch order or give me a moment to check on the status.

DR. LoCICERO: Okay. Our next speaker is

going to be Christopher Marmo.

MR. MARMO: My name is Chris Marmo. I'm the Senior Vice President of R&D for Allergan Medical, and I want to thank the Panel for allowing me to present on our safety of our Juvederm injectable gel.

First and foremost, when we develop a product at Allergan, safety is part of our key concern here especially in the aesthetic area. In looking at the safety of our products, first and foremost we have to make sure that the material we're going to be utilizing is very safe. And when we had a choice between materials that we could look at for dermal fillers, Allergan Medical chose to use hyaluronic acid as the dermal filler material, and the basis for that is hyaluronic acid is a polysaccharide that is naturally present in the skin. Also it performs multiple functions in the body such as lubricating joints and aiding cell motility.

Right now, HA is the most commonly used filler material in the U.S. and worldwide. You have to make a distinction between HA based fillers and also the other particulate fillers or semi-permanent fillers. Nearly 2 million HA treatments in the U.S. in the past two years.

So when we look at Allergan's specific dermal filler, which is behind the trademark or trade name of Juvederm, it was developed and now produced with safety as a top priority. Juvederm is not animal derived. It's produced within the Allergan facilities under very strict processes and high standards, and it is now CE marked in Europe since 2000 and approved in over 50 countries worldwide. We have approximately 2 million syringes distributed internationally, and in the U.S. alone, since the approval in 2006, we have over 1 million syringes distributed in the U.S.

So in our premarket clinical studies and also premarket preclinical testing, Juvederm was confirmed to be both very pure and also very biocompatible. We did our clinical study on 439 subjects and 160 of those subjects had a Fitzpatrick skin type between IV-VI.

What's important to note here is that since we had such a large patient population of Fitzpatrick skin type IV-VI, the FDA did not require us to do any postmarketing work in that specific area.

So in our clinical studies, we had no serious adverse events related to Juvederm treatment. Most side effects were mild or moderate in nature,

and the duration was very short lived, less than seven days. The most common side effect was redness, pain, firmness, and swelling. As I said before, those were resolved very quickly.

The study did show now increase of hyperpigmentation or hypertrophic scarring in the patients with Fitzpatrick skin types of IV-VI, and what we did note was that there was no statistical significant difference in adverse events between Caucasians and non-Caucasians.

As we look at the postmarket reports, they're very similar to what we saw in the premarket study, that the overall adverse event reported in the U.S. was 0.25 percent and the most common complaint was edema occurring at .043 percent. And we didn't see any unexpected adverse events reported that we didn't expect.

So in conclusion, Juvederm has a very impressive safety profile, prevents minimum risk to the patients based on a long history and high volume use. As we said, it's been in the European market since 2000, over 2 million syringes distributed, and then in the U.S. over 1 million syringes distributed. Low occurrence of adverse events, and the adverse events we have seen have been mild to moderate in

severity and resolved very quickly. Thank you.

DR. LoCICERO: Thank you, Mr. Marmo.

Next is Dr. Alan Gold.

DR. GOLD: Good morning. I'd like to thank members of the Panel for allowing me the opportunity to appear before you today. My name is Alan Gold, and I'm a plastic surgeon certified by the American Board of Plastic Surgery. I'm in private practice, clinical private practice in Great Neck, New York.

I'm currently President to the American Society for Aesthetic Plastic Surgery, which I will refer to from this point on as ASAPS, and I'm here today as its representative. I'm also the immediate past President of both the Aesthetic Surgery Education and Research Foundation and the American Association for Accreditation Ambulatory Surgery Facilities. I still currently serve on both of those Board of Directors and currently serve on the Board of Directors of the American Society of Plastic Surgeons.

I'd like to emphasize that consistent with the disclosure and conflict of interest policy of ASAPS, our own organization, as an officer of that organization, I can have absolutely no financial or business relationship whatsoever with any supplier,

manufacturer, or industry related to healthcare.

I'm here today with my travel and expenses paid for by ASAPS, to both support your current and future efforts in refining premarket and postmarket study designs for the evaluation of dermal fillers or injectables and to discuss some of our own current postmarket surveillance and patient safety initiatives in that regard.

As practicing physicians, we are concerned as you are with the safety and efficacy of the products we use to treat our patients. And while I realize this may be preaching to the choir a bit, we must never lose sight that it is all about the patient, not about the physician, not about industry, not about government or bureaucracy, but about the patient.

Although I'm here as a plastic surgeon, I want to emphasize that those concerns are shared by many stakeholders and that the core physician groups practicing cosmetic medicine are willing to set aside their sometimes divisive turf battles and partner with each other and with you for such issues of patient safety.

A perfect example of this I'd like to discuss with you is the Physicians Coalition for

Injectable Safety. The Coalition, a concept initiated by ASAPS in our outreach to and inclusion of the other core physician groups, was initially made possible through unrestricted educational grants from the diverse group of injectable product manufacturers who recognized this as a patient safety initiative.

The mission of the Coalition for Injectable Safety is to provide the public with unbiased and necessary information on injectable cosmetic treatments, appropriate injectors, how and where to safely access cosmetic medical procedures.

Our goals are to eradicate the practice of unqualified persons providing injections, to promote treatment supervised by properly qualified, trained board-certified physicians, including plastic surgeons, facial plastic surgeons, oculoplastic surgeons, and dermatologists, and to promote only the use of FDA approved, appropriately obtained, and appropriately administered products.

In the case of our international partners, of course, that would be reflecting as well the international applicable governing bodies of those countries.

The Coalition was created to provide the

public with accurate, unbiased, and factual information allowing consumers to make informed choices regarding medical treatments, a group representing more than 5,000 board-certified physicians across the U.S. alone.

Current key U.S. stakeholders of the group are the American Society of Prosthetic Plastic Surgery, the American Academy of Facial Plastic and Reconstructive Surgeon, and the American Society of Ophthalmologic Plastic and Reconstructive Surgery. And we hope to soon be rejoined by the American Society of Dermatologic Surgery, which was one of the original founding members of this organization.

The importance and wide impact of this effort has even been recognized internationally as evidenced by the recent addition to the Coalition of the International Society of Aesthetic Plastic Surgery, which represents surgeons in 73 different countries, the International Federation of Facial Plastic Surgery Societies, as well as the Canadian Society for Aesthetic Plastic Surgery.

Our patient safety initiatives have included issuing safety advisories, our membership in the FDA Counterfeit Alert Network, a robust website for physician and public information, and the

development of the continuing education program not only for physicians but also for nurse and physician assistants injectors. In addition, the Coalition is in the process of developing a workbook of policies and procedures regarding injectables including standardized templates for patient evaluation, injection planning and documentation, informed consent documents that disclose off-label practices such as alternate site injections, adverse event reportings, quality improvement and patient satisfaction. Also in development is a section on infection control and safety engineering to prevent possible injection errors and promote best medical practices.

We would welcome the FDA's review of these documents when they are completed which should be in the very near future.

And this serves as but one example of our ability and commitment to work across specialty in that it's for the public good.

We in ASAPS are in full accord with and wish to emphasize the recommendation that you will soon hear from ASPS for the formation of a broadly based consensus panel of diverse stakeholders to partner with the FDA to help address the complex

issues before this panel today, particularly regarding pre and postmarket evaluation of dermal filler devices.

We are committed to the practice of evidence-based medicine and appreciate the need to not only carefully study the safety and efficacy of devices, but also the need for outcome studies to measure quality of life improvement, patient satisfaction and the attainment of objective and definable aesthetic goals. We have, in plastic surgery, made what I believe is an impressive progress in the development of tools to facilitate that analysis as exemplified by the -- work of researchers such as Dr. Pusic in the development of her outcome study tools which you'll hear later today about in greater detail.

ASAPS is also actively involved in the as yet more abstract development of measurable standards of beauty and objective aesthetic outcome measures, incorporating input beyond our own aesthetic expertise from artists, philosophers, psychologists, anthropologists and the like. To the extent that our findings might assist in the applicable efficacy outcome measures within the purview of this Panel, we would be pleased to share them with you.

I want to compliment the Panel on the Executive Summary providing us background for this meeting as well as for the incisive patient questions it is to consider. Although I don't mean to presumptuous, I would like to propose some opportunities in response to but a single of those questions at this point.

And that is, what would be the most efficient method or combination of methods for FDA communication to physicians regarding postmarket information collected by the FDA? Such as information on adverse events, et cetera.

Speaking on behalf of the American Society for Aesthetic Plastic Surgery, I'm pleased to offer you consistent and guaranteed communication of that information through four vehicles. One, our member newsletter, ”Plastic Surgery News," and the websites of not only ASAPS but of the Aesthetic Surgery Education and Research Foundation, and on behalf of our Coalition partners, that of the Coalition for Injectable Safety. By extension, I would hope to be able to provide you with the same access to the websites of all of the various partners of that Coalition. That would provide the addition of wide and essentially immediate access to both the medical

community and the public particularly critical to the dissemination of your urgent messages, although again I'm presently speaking only for ASAPS. Perhaps we could partner with ASPS or even some of the other cosmetic medicine core of physicians to use not only the websites but their publications for dissemination of such important FDA information, and ASAPS would be happy to investigate that potential and coordinate such an initiative if the Panel feels it might be helpful.

I'd also like to offer the FDA a unique opportunity to have such information regularly published in the Aesthetic Surgery Journal or ASJ, the peer reviewed and indexed official scientific journal of ASAPS, and especially designated and reserved FDA section. It would be consistently available to you but only on an as-needed basis and without obligation. In other words, the FDA would have guaranteed regularly reserved access to our readership with the accessibility, credibility, and power of an indexed journal for its scientific information to be incorporated into the world literature to be used if, when, and as you see fit.

Even more importantly, an Executive Summary such as that provided for this meeting and any

recommendations of this Panel, the study structure and the benchmarks for premarket evaluation and postmarket surveillance would be considered valuable scientific contributions worthy of publication and wide dissemination. We believe such FDA collected postmarket information on adverse events, et cetera, would provide welcomed, unquestionable, unfiltered, independent and critical data without potential questions of a for profit investigator or industry bias and all these additional communication opportunities, of course, at no cost to the FDA.

In conclusion, I appreciate the appreciate the opportunity to appear before you today and want to once again emphasize our support for your efforts and the willingness of the American Society for Aesthetic Plastic Surgery to work collaboratively with you and all other interested stakeholders for the benefit of the public. Thank you.

DR. LoCICERO: Thank you, Dr. Gold.

Dr. D'Amico, are you prepared now?

DR. D'AMICO: Yes, sir. Good morning, and once again, thank you for your indulgence, Dr. LoCicero.

Thank you for allowing me to be here today. My name is Richard D'Amico. I'm a board-certified

plastic surgeon practicing in Englewood, New Jersey. I'm the Chief of the Department of Plastic Surgery at the Englewood Hospital and Medical Center, and I'm assistant Clinical Professor of Plastic Surgery at the Mt. Sinai School of Medicine in New York City.

I'm also the immediate past President of the American Society of Plastic Surgeons. I too have served on the board and continue to serve on the board of the American Association for Accreditation of Ambulatory Surgical Facilities.

In terms of disclosure, I have served on a Medicis Advisory Board for one day in September of this year. I have no other financial ties to any corporations manufacturing these products. My travel today has been paid by ASPS.

I would like to briefly address the Panel regarding long-term safety and effectiveness of dermal fillers and what ASPS along with our colleagues at the American Society for Aesthetic Plastic Surgery, as you just heard from Dr. Gold, are doing to help ensure patient safety, and as Dr. Gold mentioned, my colleague, Dr. Andrea Pusic, will address you later today regarding plastic surgery's innovations in developing a validated web-based tool for patient reported outcomes, the Breast-Q for

breast surgery and subsequently the evaluation of Face-Q for facial aesthetics.

In recent years, as you know, there has been a dramatic increase in both the number of fillers and the number of patients seeking minimally invasive procedures. According to ASPS procedural statistics, minimally invasive cosmetic procedures rose by nine percent in 2007 to nearly 10 million procedures. With the increase in demand, hyaluronic acid fillers alone jumped from the fifth most popular procedure in 2006 to second in 2007. Cosmetic minimally invasive procedures for the face increased considerably for both women and men.

These statistics demonstrate remarkable growth in less invasive cosmetic medicine procedures. One could infer an association between the increased utilization of these products and growing patient awareness and satisfaction with the results that these less invasive procedures provide. But we believe the data also represent an obligation for continued vigilance in measuring patient experience and working to ensure long-term safety and effectiveness.

ASPS believes that it is critically important for patients to consult qualified

physicians such as plastic surgeons, dermatologists, ophthalmologists and ear, nose and throat physicians. Dermatology and plastic surgery are widely recognized as the clinical practice and research experts in minimally invasive cosmetic medicine. The specialties of ophthalmology and laryngology are also important stakeholders.

ASPS is interested in working with key stakeholders in the soft tissue filler arena to convene a consensus conference for assessing the long-term safety and effectiveness of dermal fillers. We are particularly interested in developing appropriate study designs for the ongoing evaluation of emerging technologies in cosmetic medicine. We are committed to ensuring that safe and effective therapies and devices are available to patients.

While the development of emerging technologies is pivotal to the advancement of medical practice, we realize that those involved in healthcare, both clinicians and organizations, can and should play a key role in establishing criteria for the ongoing measurement and evaluation of existing therapies.

Each year, millions of less invasive aesthetic procedures are performed in the United

States, but the current body of standardized research and measurement criteria for these procedures is, as you well know, limited. In particular, facial aesthetics is an emerging area where we believe a coordinated cross-specialty and disciplinary approach for establishing consensus on research study design and clinical endpoints is absolutely needed.

We are interested in the Agency's feedback on the formation of such a multispecialty consensus conference charged with the primary goal of establishing standardized criteria for measuring safety and effectiveness of procedures and devices used for facial aesthetics particularly in the long term. A panel composed of key physicians representing related medical specialties as you've heard today performing procedures and research in facial aesthetics together with industry, consumer advocates, government agency stakeholders and technology assessment and health services research experts, will work together to develop a coordinated research agenda as well as planning to address the measurement challenges related to facial aesthetics.

My colleague, Dr. Pusic, as I mentioned earlier, will present some of this date regarding Breast-Q later today.

Developing consensus for a coordinated research plan will allow stakeholders to best utilize available resources, develop appropriate universal measurement tools and criteria and avoid duplication of effort. We have reached out to our colleagues in this country as you've heard before me, to the dermatology community, and as Dr. Gold described, across medicine and have a broad willingness to participate. We've reached out in Europe where we have a cooperative joint European meeting in Paris in April of 2009, and have received tremendous willingness to participate. Dr. Gold has already alluded to some of the international societies that are interested in part of this effort.

To begin, we propose convening a consensus panel for the purpose of presenting background on the current state of clinical practice and literature related to facial aesthetics, reviewing issues related to new technology adoption, discussion of appropriate clinical endpoints and their measurement as well as short and long-term priority research areas such as granuloma formation and biofilms.

Developing widespread consensus on short and long-term clinical endpoints and the measurement tools and methods will allow both prospective and

retrospective studies to capture the same information when appropriate, an increased statistical significance in answering important questions.

The advantage of the consensus approach at its full implementation is the development of a coordinated effort across the field to facilitate meaningful study design, data collection, measurement and analysis.

We understand that it has been a challenge for the FDA to develop postmarket studies to demonstrate long-term safety and effectiveness, given the evolution of these products and their emerging uses, particularly in the arena of off-label use.

We stand ready to work with the FDA to determine whether postmarket clinical studies can develop a more effective process for updating the labeling of certain products. Postmarket surveillance studies are a key element in providing patients with additional assurance that their health and safety are assured.

Plastic surgeons are committed to continuous quality learning and quality improvement. Indeed, quality and patient safety are cornerstones of the plastic surgery community.

In addition, ASPS has strongly encouraged

and will continue to encourage our members to participate in postmarket studies.

As always, we stand ready to assist the Agency as appropriate in taking steps to assure the long-term safety of dermal filler.

We look forward to our continuing partnership with FDA. We offer you all of the communication modalities that Dr. Gold described in terms of disseminating FDA information to our members both here and abroad.

Thank you for the opportunity to address the Panel.

DR. LoCICERO: Thank you, Dr. D'Amico.

Is there anyone else in the audience who would like to address the Panel at this time? Please raise your hand and come forward.

DR. KLEIN: I have a presentation that I'd like to present.

DR. LoCICERO: You have five minutes.

DR. KLEIN: -- five minutes. I've spent 30 years -- First, you have to show me how to use this machine.

I disagree with a lot of the -- because I think there are problems with understanding the scientific basis for what's happening. I do have a

presentation -- about. I think we have to understand how these agents perform under the skin, and I think that's -- Also I think you have to be very careful when you use non-biologics under the skin.

Okay. I'm Dr. Arnold Klein, a Professor of Medicine and Dermatology at UCLA. I have an endowed chair in my name at UCLA, and I've been injecting fillers for three years.

So we talk about a newly invasive aesthetic, and basically what we're talking about is really in the 21st Century of art and science to find medicine at its best, and medicine at its best is really raised to an art -- and this is -- and things like that but you must have a science.

Now, these are things I have developed, the technique of injecting collagen. You have to have a skin test collagen. I've got all kinds of lip enhancement. I've used Botox from Brazil, Argentina, France, Japan, Korea, Italy and also developed Botox injection patterns and dilution that was used in the clinical trials, the manner in which it's used for crows feet, the manner for which is used for the upper face treatment, also developed the manner for which it's used at the corner of the mouth, as well as its use in -- I developed the technique for

which hyaluronic acids are used and restoration of -- face and the injection of -- So I have not been not busy at this time.

This is my textbook where they define me as the undisputed teacher and pioneer in the soft tissue field. Unfortunately I'm no longer able to lecture. This is a video, and I've explained to you why that happened.

This is all about volume restoration. We know that already. We're talking about fillers today, but what is the clarification of a filler. You have to have a high use potential but a low abuse potential. And you must have it biologically pure. So you don't want anything synthetic under the skin because the body's not going to know how to handle it. You want it to be non-allergenic, low protein -- doesn't cause cancer, must not cause inflammation. That's very critical, and ease of storage, and you want the integrity of the scientific data behind it that you present with it, and that's the most important.

Now, remember -- we inject is the lip, and I started that in '84, and there's a certain shape to it that one must know. So if you start to evaluate a study pattern, a design, you must show the proper

shape of the lip, understand aesthetics. So this is before and after injecting the lip -- This patient I pulled the skin forward in doing this. It took me an hour to inject this, and this is what I'm capable of doing.

And this is a study design of what I saw because if you take one page out of the study and you begin to look at it, notice what they do in the study. It's a study of the use of Juvederm for example, it could be any type, but they compared it with -- notice all the problems they had with firmness, redness, swelling, pain, tenderness and lumps besides that. Now, if you have that many problems with injectables, do you know what that means? You don't know how to inject. So one of the key things is we have to have people who know what they're doing with a needle under the skin.

Now, we have now what I call the invasion of the -- because basically up to a certain period of time, I was the world's authority. But then came a whole group of politicians in dermatology that took this field away from me, and basically we're going to talk now about the -- fillers. The consequences have long-term problems. We knew that basically when the Federal Government made silicone illegal and because

facial contours change over time, it has become more visible to create an unnatural look. The -- are difficult or impossible to correct. So it's a really important question whether we should even have these permanent or semi-permanent.

The first one I'll talk about is ArteFill, and basically the FDA Panel has really a poor understanding of this because I'll tell you what I think the understanding should be. There was no one that showed the histologic evidence of how this agent performance under the skin. So how can you base it on anything because the structure and the function of the skin is very important. When you put an agent under the skin that causes inflammation, you must know that, but nowhere in the study of this agent was that done. The product approval must also go before the Panel. There's been a number of agents approved by the FDA that were never presented in front of the Panel. And you also have people reviewing the data, you know, on adverse reactions, but I will tell you this. Physicians are not reporting them yet, so we really don't know the true incidence. And we are not taking worldwide data into consideration.

When this agent was passed at the FDA, none of the physicians presenting the evidence were

Americans. Yet, Cecilia Watkins would not allow me to present to her, which I objected at the time, all the worldwide data that showed this had been problematic because I had traveled over them.

So in 2003, in a dermatologic journal called Occurrence, a group of doctors said how wonderful this product was. Yet, this product was already being told by the Swiss and German governments I recall to be disastrous.

DR. LoCICERO: Please conclude now.

DR. KLEIN: I can't conclude. Sir, I said I'm disabled. I came a long distance from California on my own money. I need to speak a little bit more because I'm going to make sense --

DR. LoCICERO: Thirty seconds.

DR. KLEIN: We're going to save lives.

DR. LoCICERO: You have 30 seconds.

DR. KLEIN: Thirty seconds to save lives? I have 30 seconds to save lives. Okay.

All these agents, and we're talking about Sculptra, we're going to talk about the agent called Radiesse, and we're going to talk about those two.

In Sculptra, in the studies that were used, in individuals with HIV, 55 percent of them developed nodules. None of that was presented to the FDA. And

it caused these nodules in multiple individuals. Radiesse also causes lumps when injected under the skin, particularly in lips. Now, Sculptra is only approved when used in HIV-positive individuals, but they have not kept to that and the company is -- specifically to that. So what you have is here is the control. Because I made a statement that was against what the Dermatologic Society was doing, I'm not allowed to lecture there, and you have agents that you have approved that you have no idea how they function under the skin.

DR. LoCICERO: I'm sorry.

DR. KLEIN: All these agents, let me say one last thing, supposedly cause neo-cologenisus (ph.). Not one of them has ever been shown to show neo-cologenisus. All they cause is foreign body inflammation, which is the worst thing you can cause with a filling agent. Thank you.

DR. LoCICERO: Thank you. Are there other individuals who wish to address the Panel?

(No response.)

DR. LoCICERO: I want to thank all of the speakers for their comments, and we will take those into consideration as we deliberate.

Next, we're going to have an update from

Dr. Krause on the FDA since the last meeting.

DR. KRAUSE: Good morning, everybody. My name is David Krause, and I'm going to update you on things that the Division has done in the area of general and plastic surgery since the last time we had a Panel meeting, which actually was quite a while ago.

The last meeting we had was August 24 and 25, 2006. So you can see it was more than two years ago. During that Panel meeting, the Panel recommended approval for BioForm's Radiesse for treatment of HIV associated lipoatrophy as well as for nasolabial folds. The third topic that was discussed at that panel meeting was the reclassification of the cyanoacrylate tissue adhesives or tissue adhesives in general for use in approximation of skin.

Since then, since that Panel meeting in 2006 September, we approved a product called Medafor, a product manufactured by Medafor called Arista AH which was approved as an adjunct to hemostasis.

In October we approved the Artes Medical Product, ArteFill, for correction of nasolabial folds.

In October of 2006, we approved two PMAs,

one from Allergan and one from Mentor Corporation for a silicone gel filled breast implant and the specific indication was augmentation for woman at least 22 years of age and for breast reconstruction for women of any age.

In December 2006, we approved the Anika Therapeutics filler material that at that time did not have a name. It was simply called cosmetic tissue augmentation product.

Also in December we approved two PMAs for BioForm Medical's Radiesse.

In February of 2007, we approved Histoacryl for topical adhesive for skin closure for skin that was minimum tension wounds.

In June 2008, we approved a PMA which was submitted to us by Johnson & Johnson for a filler made of collagen named Evolence, and again it was for wrinkles and folds such as nasolabial folds.

We also took action on your recommendation regarding the reclassification of the tissue adhesive for topical approximation, and in May of 2008, we issued a letter reclassifying those products from Class 3 to Class 2.

A few 510(k)'s of interest. These are clearances, not approvals. There were all over-the-

counter uses. So that's what made them interesting. We cleared the Palomar Medical Technologies ABC light-based hair removal system, which is indicated for intended use of adjunctive use with shaving for hair removal sustained with periodic treatment.

In February of 2008, we cleared the Life BioScience LLC's GentleWaves consumer LED, and the device is indicated for periorbital wrinkle reduction.

In March of 2008, we found as substantially equivalent Photo Therapeutics New-U product, which is intended to emit energy in the red and IR region of the spectrum to be used in dermatology for treatment of periorbital wrinkles.

And in November of 2008, we cleared the Pharos Life Corporation's Tanda Skincare System, which is indicated to treat dermatological conditions. Specifically a blue light is used to treat mild to moderate inflammatory acne.

I'd like to just give a quick overview of a new program that the FDA has introduced since the time of our last Panel meeting, which we call the Matrix. Normally FDA has many offices and information usually flows down the office from the director of that office down through the divisions to

the branches to the individual reviewers. And sometimes it's difficult for the right hand to communicate with the left hand.

So Dr. Schultz, who is the Center Director, has initiated a program which he calls the Matrix which allows for crosscutting between offices, and the overview of what the Matrix does is listed there. And the purpose of the Matrix is to identify and communicate problems and risks, identify and communicate when perceived issues are not public health concerns soon and more clearly, and to assist with the integration of pre and postmarket activities.

And I just wanted to point out that this is actually a good way, the Matrix, for individuals to get information to the Agency, and so I'm going to put up the names of the two individuals that our particular branch interacts with and their e-mail as well as their phone numbers are on the screen. Ann Ferriter normally deals with the more general surgery type issues whereas Nada Hanafi works with the plastic and reconstructive procedures which would be the fillers which we're discussing today and also breast implants. And I thank you.

DR. LoCICERO: Thank you, Dr. Krause. The

Chair apologies for missing the presentation earlier.

So the Panelists should now have an opportunity to ask questions of the public speakers if you have any. Now, would be the time.

DR. BIGBY: I'd like to ask Dr. Gold, you made a statement about restricting the use of fillers to qualified physicians. Would you describe what it is you had in mind to accomplish that?

DR. GOLD: I think that was actually a comment made by several others, but I think that we have to be in compliance with not only the laws of each individual state which differ but also the realities of the marketplace. And the realities of the marketplace are that while many of us prefer to give our injections to patients for fillers that are toxins, there are areas of the country, states, in fact, that allow the injection by non-physicians, either nurses, physician assistants, or sometimes even trained technicians of those injectable products and with varying supervision requirements for individual physicians to either be present or immediately available.

We would be disingenuous if I was to tell the Panel that there are not physicians that delegate that kind of work to physician assistants or non-

physicians under their oversight, but we have a commitment to train not only physician members of various core specialties, dermatology, facial plastic, oculoplastic, and plastic surgery, but also the nurses and physician assistants that would be working under them to provide the best possible injector training programs for all of them possible, and the members of the Coalition have made that commitment to do so.

We would not presume to be able to legislate or request legislation for the restriction of access to care under any of those different professions, but we would certainly prefer. I would personally prefer, and I think it's split amongst our organizations, that physicians only be allowed to do the injections, but that's not the reality of what goes on in this country. And because of that, we've taken it upon ourselves to try to create a teaching system, a training system with continuing education for all potential injectors. Thank you.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I would just like to ask Drs. Gold and D'Amico. I'm a little unclear. Dr. Gold, you alluded to the Physicians Coalition for Injectable Safety, and Dr. D'Amico, you talked about

a consensus conference. Are these the same or are these two different things, or could you just clarify this for us?

DR. GOLD: Thank you. There are two totally separate items. The Physicians Coalition for Injectable Safety is a consensus organization of the very specialties that I mentioned. That's different from the convening of a consensus group to specifically deal with the issues now before this committee today, and we are supportive of that. ASAPS, which I'm speaking for now, is supportive of that consensus meeting to be held, the consensus group, as proposed by Dr. D'Amico. The two are not related.

DR. D'AMICO: If I might, Dr. McGrath, I want to be clear, and I apologize if it there was a lack of clarity. What we're proposing is something, is a consensus conference that would address long-term safety and effectiveness, research proposals, looking at complications, looking at effectiveness in large populations over time, the sort of thing that you can really only get out of a longer postmarket type surveillance, and we envision this as multispecialty, multidisciplinary with industry, consumers, with everybody at the table, so that we

can get the best outcomes for patients long term.

DR. LoCICERO: Dr. Anderson and Dr. Newburger.

DR. ANDERSON: Yes, I have a question for Dr. Gold and Dr. D'Amico as well.

Regarding training in off-label use, do you have -- first of all, do you have a plan or a proposal to suggest to the FDA regarding appropriate training for all people who might be injecting, and do you have a training plan for off-label use?

DR. GOLD: Well, I don't have a specific proposal for that training program. It would hopefully be one that would mirror the training program that we have created already, and I'd be happy to share that information with you in terms of exactly what's done, how it's done, where it's been done, who's been trained, et cetera.

That still doesn't obviate the need for long-term follow-up studies. Of those trained injectors, experience with the fillers as we said before, I think one thing that the Panel appreciates which needs to be restated again is that these fillers are tools. You don't get the same result with a filler injection by one individual as compared to another. It's a different skill level as much as

you see in surgery. Everybody has the same access to a scalpel, and the results are very different. They may have the same basic training but sometimes have greater complication rates, and the same thing may be true even with trained injectors, but certainly we try to level the playing field a bit and provide the greatest assurance of patient safety if we can provide that basic training for injectors.

And the other question you had raised was suggestions in terms of off-label use.

DR. LoCICERO: Mr. Melkerson, before we get into that, you should make a comment.

MR. MELKERSON: This is Mark Melkerson, Director, Division of General, Restorative and Neurological Devices.

The issues of off-label abuse, FDA regulates the manufacturers and the labeling of their products that have been approved for use. The use of products that are off-label, as an individual, you as a surgeon have the right to use any medical product according to what you think is in your patient's best interest with their consent, but in terms of a manufacturer, that is one of the reasons for the afternoon session which is all those types of indications that are outside the approved labeling,

what types of studies, what type of questions should we be asking for those companies that are now pursuing those indications that are not currently part of the approved labeling.

DR. D'AMICO: Thanks, Dr. Melkerson. Dr. Anderson, you bring up a good point, and I think this is where this is something that would be on the plate of a consensus conference, you know. We understand that initial studies have to be focused, but long-term studies can have a broader base and incorporate the natural progression of medical science and off-label uses are part of that process, and clearly as teachers and patient safety advocates, the professions are ideally positioned to incorporate these other uses over time and to teach our colleagues the proper way to incorporate these advances in other uses.

So that is envisioned as part of the profession's responsibility with this type of conference.

DR. GOLD: And just one further thing on that. And that's why the deliberations of this Panel are so very critical for us and for our patients because many of our physicians will take the responsibility on themselves to use a product off-

label, suddenly thinking they have the brilliant idea, that it can be used to augment one other body part or another and don't have the access to a worldwide experience of long-term follow-up reports of the potential complications of the use of those products by people who thought independently, they decided it would be reasonable to augment other areas for fillers.

I think the outreach by the FDA to get the communication out to the practicing physician of those long-term studies adverse event reports is absolutely crucial, and that's why both Dr. D'Amico and I and I'm sure the other core specialties involved are so willing to incorporate this into our communications. It's critical that physicians who are taking it upon themselves to use these products that may give the product a bad name be made aware that other people may have done it as well and learn by their experience. So, you know, I think the reporting of those adverse events is very crucial for us, and the way to design the studies obviously is the purview of this Panel, but it is a significant issue for us in terms of off-label usage.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: Dr. Gold, I visited the

injectablesafety.org website, which is clearly sponsored by a number of companies that manufacture aesthetic devices, and it says it's an unrestricted grant. And I scanned the numbers of products that were listed, and under it, it seemed like there was a tremendous list of the off-label uses for these products, and it almost seems like an exhortation that you could or it has been used in these areas. I think that might be a good place to talk about some of the pitfalls of using it off-label, but the way I read it was someone looking at this might say, oh, okay, I'm going to give it a try here because that's listed. So I wonder if there could be a few more caveats on that.

DR. GOLD: Absolutely, and that's why I would welcome participation of the FDA to provide information through that site on those adverse events. I think the reason that those are listed is because it's a public website as well, and not just for members of the organizations, and I think it's a way of trying to get reliable information out there. It's not that it is being promoted by any industry supporters, and again, those are unrestricted grants that have nothing to do with what's on the website whatsoever. But again, with a view towards patient

safety, the use off-label for almost all of the injectable products is greater than the arm label usage for the specific area under which it was initially approved, and we have to deal with those situations. Certainly your point is well taken, but it is the intent to incorporate into that website those adverse events and caveats as well.

DR. NEWBURGER: Who wrote the off-label uses? Who listed them there?

DR. GOLD: Specifically who?

DR. NEWBURGER: Was it a member of the specialty organization?

DR. GOLD: Yes, there is a group of physicians who has direct oversight who agree on virtually everything. It's a consensus run site and organization. So there would not be anything put on there by one individual organization without the oversight and approval of the others.

DR. NEWBURGER: Thank you.

DR. LoCICERO: Ms. Rue.

MS. RUE: Hello. You asked a question. You've spoken briefly about consumer education, and I think the Coalition talked about making sure that the consumer was educated. Can you briefly address what avenue you've done to address this issue?

DR. D'AMICO: I think our website, plasticsurgery.org certainly is available to consumers for education. Dr. Gold has discussed the injectable safety website, and I think that what you're hearing here is a willingness across the entire field of medicine to step up to the plate and take a leadership role in the educational piece, developing the right research tools, helping the Agency to come up with appropriate clinical endpoints so that all this can get done and you're absolutely right. We need to keep the consumers informed every step of the way. We also are available to the media and try to make ourselves available and through them, educate the public. They're very powerful in terms of their reach, and I know that in the last year, I've done 105 national media interviews, and I would say that 75 percent of them have to do with facial aesthetic issues and cosmetic medicine procedures. So it's something they're very sensitive to.

DR. GOLD: And specifically in response to what we've done for the public, as I briefly alluded to in my presentation, we're presently developing a workbook through the Injection Safety Coalition, the Coalition for Injectable Safety, which will incorporate, expand, and inform consent documents

discussing off-label usage, and the risk associated with those off-label uses in various areas of the face, body and with a number of different injectables. They're in the process of being done now, and again I offer to share them with the Panel for their review before we put them out and for your input, but those type of patient safety initiatives are ongoing.

DR. LoCICERO: Dr. Li.

DR. LI: Steve Li. The reporting of adverse events of medical implants of all types has been notoriously and historically almost impossible endeavor. For instance, in the orthopedic devices for which I'm most familiar, our estimates that far less than one percent of the actual adverse events are actually reported to the FDA.

Do you have some program or some insight or some system or protocol that you can envision that would actually solve this problem?

DR. GOLD: I don't know if it would solve the problem, but again as part of that work through the Injectable Coalition, we are developing protocol for adverse event reporting which we would encourage all of the member organizations to promote to their membership. I think that we were able to witness

something that we really didn't know we could deliver on in respect to the vesting plant postmarket surveillance and the reporting of all of our member physicians or the majority of our member physicians to enable completion of some of those studies.

I think it would be the same with this. Once we develop the templates for that adverse event reporting information to be gathered, we look to do that cross-specialty and if we're able to develop it, and again I'd welcome the input of this organization in those -- in the formulation of that reporting document. I think we will try to gather better information as was said earlier and, you know, you just substantiated so very few of the potential adverse events are reported. It's true that those that aren't reported are the minor, short-lived transitory adverse events. I don't consider swelling after an injection to be a significant adverse event. I do consider skin loss or infection or nodule development or deformity, et cetera, to be a significant reportable event, and we're developing the structure for those things to be reported. We're not there yet, but we're working on it.

DR. D'AMICO: I'm glad Dr. Gold brought up the breast implant issue because it's something with

which we have a lot of experience, and certainly what we've been able to reach with our plastic surgeons is, as a society to develop a culture of participation, and I alluded to that. We're actually developing programs to teach our plastic surgeons to become better investigators, better researchers. So they're not just clinicians, but they're comfortable investigators, and that culture starts to look at all the data as being precious for patient safety, and I must say in all fairness though, there are some social witch hunts out there that occur from time to time that inhibit physicians from reporting adverse outcomes, and it shouldn't, but it's a reality.

So I think what we're trying to do societally is -- and I think the best implant issue is a success or will be a success, that we're making the numbers that physicians are participating and part of that is getting the date. Part of data is adverse outcomes. It is just all about data and outcomes. We've developed a mechanism for developing data called tracking outcomes in plastic surgery over the last five years where we can now real-time monitor members' practices, and the whole idea is we gather the data real-time as it comes in with all the data, including adverse events.

The accrediting body that I mentioned in my remarks and that Dr. Gold mentioned has mandatory real-time online reporting requirements for adverse events. So I think we've made a lot of steps in developing a culture in our specialties and across our specialties to have physicians step up, that the data is critical for patient safety, all the data is important.

DR. LoCICERO: Are there any other questions? Yes, Mr. Halpin.

MR. HALPIN: Given the leadership role that you have in the academic community, I just wondered I you might give a couple of words on your ability to cooperate with industry and the FDA in terms of developing guidance for dermal fillers more specifically and willingness to do that.

DR. D'AMICO: Certainly. And that would be the focus of the consensus conference. In this particular moment, I'm not just speaking for the American Society of Plastic Surgeons, but we've had discussions with the American Academy of Dermatology. We've actually shared these ideas offline with industry, and we've been given very positive feedback on this.

Frankly, we feel it's time for the

specialties, for medicine to step up and take the lead. I think that's what patients expect. I think it's in their best interest and, of course, we have to cooperate with industry. They need to be at the table. Consumers need to be at the table. So this consensus conference would be a very big tent, and we would actually seek the Agency's certainly cooperation, approval, whatever this Panel and the Agency decides to do.

But we feel this would be a step forward in coordinating and organizing long-term data on patient safety.

DR. LoCICERO: Are there any other questions from the Panel?

(No response.)

DR. LoCICERO: Thank you very much.

We'll now hear the FDA presentation. At the conclusion of the presentation, there will be time for questions from the Panel members.

At this time, we'll hear from the FDA speaker, Dr. Jiyoung Dang.

DR. DANG: Good morning. My name is Jiyoung Dang, and I'm a reviewer in the Plastic and Reconstructive Surgery Branch within the Office of Device Evaluation, and I'll be presenting, as well as

coordinating, the presentations on behalf of the FDA.

Today's discussion focuses around dermal filler devices, and this is a general topic, non-device specific discussion. One of the main goals of today's meeting is for FDA to seek input from the Panel regarding topics on clinical study design both within the premarket and postmarket realm, device labeling as well as modes of communication between the FDA and the public.

The FDA presentations will encompass review of postmarket data currently available to the FDA that include both adverse reports as well as post-approval study data, as well as a summary of clinical study designs that FDA has approved thus far for premarket approval as well as clinical study considerations for possible new indications for use.

To begin, I wanted to have an introduction of dermal fillers that have been approved by the FDA to date. They include both non-observable as well as observable dermal filler materials and synthetic and natural materials as well. One of the observable materials is the polymethyl methacrylate, microspheres suspended in a carrier gel manufactured by Artes Medical. We also have observable synthetic materials such as hydroxylapatite suspension

manufactured by BioForm Medical. We have poly-L-lactic acid manufactured by Sanofi-Aventis. We have several different products under the hyaluronic acid class, and here's a listing of those materials. They're available cross-linked and with or without lidocaine. Similarly we have a range of collagen-based materials available on the market.

The general indication for use for dermal filler devices, including injection to the mid to deep dermis, is for the correction of moderate to severe wrinkles and folds. Currently there is one device that is specifically indicated for the correction of nasolabial folds, and there are two devices approved for the restoration and/or correction of signs of facial fat loss in persons with HIV, and one of these devices is also indicated for the correction of wrinkles.

Some contraindications that are common to all dermal fillers are for patients with known sensitivities to the filler material, patients with a history of severe allergy or anaphylaxis, as well as patients with bleeding disorders.

Some general warnings and precautions that are present in most dermal filler labeling include avoiding injection into blood vessels; injection

being deferred until inflammation has been controlled or resolved; injection into patients with a history of previous herpetic eruptions may be associated with reactivation of the herpes; the safety and effectiveness of device injection for lip augmentation have not been established; the safety in patients susceptible to keloid formation; hyperpigmentation and hypertrophic scarring has also not been established; and long-term safety and effectiveness of the device beyond the duration of the clinical study have not been investigated.

The dermal filler labeling includes a summary of the clinical studies that have been reviewed by the FDA for filler material approval, and it also includes the adverse events observed during that clinical study. It lists incidence rates of the most adverse events, generally the ones with the highest rate of incidence from patient diaries as well as physician case report forms, and they include adverse events such as pain, erythema, swelling, bruising, pruritus and induration. And corresponding with this is also listing of the duration of the adverse events which are generally counted from the numbers of days from symptom onset until resolution.

This is a graphical representation of

statistics taken from the American Society of Plastic Surgeons' website. They indicate the number of procedures, and there's approximately a 100 percent increase in dermal filler use between the year 2000 and 2006, and a continued increase between 2006 and 2007, and to put these numbers into a little perspective, the first dermal filler was approved by the FDA in 1981. A majority of the dermal fillers approved was after the year 2000, and of those, approximately five dermal fillers were approved in 2006.

This is a summary of today's breakdown of the FDA presentations. There will be a morning session as well as an afternoon session. The morning session will be postmarket data mostly. We have Nasrin Mirsaidi from OSB presenting a postmarket analysis of adverse events reported to the FDA. We have Ms. Azadeh Shoaibi presenting a post-approval study of dermal filler use.

Following each of these presentations, they will be open for questions from the Panel, and following both presentations, there will be a presentation of FDA questions and Panel discussion after a short break.

And the afternoon session will mostly

consist of a presentation of clinical study design consideration followed by a presentation of FDA questions and Panel discussion.

So I'd like to now introduce Ms. Nasrin Mirsaidi who is from the Division of Postmarket Surveillance within the Office of Surveillance and Biometrics, and she'll be presenting Injectable Dermal Implants Adverse Event Reports Analysis.

MS. MIRSAIDI: Good morning, everyone. My name is Nasrin Mirsaidi. I'm MDR Reviewer in Office of Postmarket Surveillance, Office of Surveillance and Biometrics. I will present MDR analysis of injectable dermal implants.

Today my presentation will start with a brief description of Medical Device Reporting System as general and its limitations, and then I will go over my research methodology and present my findings and a summary of the analysis and then present my questions to the Panel for consideration.

Our Medical Device Reporting System is a nationwide passive surveillance system through which we receive about 175,000 reports each year. It includes mandatory, voluntary, and a network of hospitals called MedSun.

Our mandatory reporting system is comprised

of manufacturers and importers and user facilities who are mandated to report adverse incidents to us.

Voluntary reporting system called MedWatch is open to public. Anybody from healthcare providers to consumers, patients, and their family can report to FDA adverse events through phone calls, fax, or online.

MedSun is medical product safety network that CDRH launched in 2002. Over 350 hospitals are member of this network and trained representative in each site regularly report adverse events to us. In general, the 175,000 reports that we receive are 95 percent from manufacturers and importers and 5 percent from voluntary reporters and user facilities.

Limitations of MDRs are relevant to everybody. It's underreported as we see. Millions, hundreds of procedures are done, but we get a fraction of them. They're incomplete usually. They don't come with complete information, patient or device identification, and we don't have the total validated data.

We cannot obtain any incidence rate because of the incomplete numerator and lack of denominator. Manufacturers usually don't give us the information exactly how many of those devices were used in the

patient. The information is biased, and because we have reporting variations and narrative variations, we tend to get a lot more MDRs when a device problem becomes public, national news, or we have a recall, and the narratives in the reports are different than who is reporting it. If it's voluntary reported, it's a totally different narrative than what the manufacturers are telling us.

And then they lack device failure analysis because most of the time devices either are not returned to the manufacturer for analysis and testing or they're discarded or they remain in the patient.

Now, I go over my methodology. For my database search, I used two criteria. One was product code and the other was date of reports received by FDA.

The product code is a three letter unique identifier that is dedicated to each device that is approved in FDA and the product code for injectable dermal implants was LMH, and we decided to capture six years of data from January 1, 2003 to September 20, 2008. About more than thousand reports was generated individually, and when fine tuned, only 930 of them remained for analysis.

When I was looking at the reports, I

realized too many terms was used for specification of site of injection and too many terms used to describe the adverse events. To bring them to a manageable number, I had to categorize them into limited number of groups. So I have about 9 different sites of injection and 11 different groups of adverse events. As was mentioned earlier, this analysis is on a class of devices and not specific to any brand names.

This slide shows the receipt of the number of reports received from 2003 to 2008, and as was mentioned, in 2006 five new products came into the market, and 2007 it picked up a little bit, and 2008 it's just to September 20. We are expecting that to be higher than that.

Overall counts, thank God we didn't have deaths. Injury reports were most of the reports at 88 percent, malfunction was 10 percent, and some of the reports were listed as other, 1.5. I will explain those later.

Source of the reports were as expected, manufacturer 94.3, voluntary reports 5.7 percent, and user facility we didn't even have any because these procedures are not done in hospitals. They are mostly in clinics and doctors' offices.

Event locations, as expected again, U.S.

had the most reports, but we had from foreign countries 14.5 percent; European countries, Japan, China, Brazil, Australia, all were included.

This is patient characteristics, even though I talked about -- this is a good representative of population out there, and most of our patients were between 50 to 60 years old, and the gender was female in 94.9 percent.

Limitations of this data analysis other than what we explained about in MDRs in general, these MDRs have their own limitations. For example, patients received multiple injections in different sites, but the adverse event was not mentioned to which one of the sites it was related to. Patients received multiple brands of dermal implants at once, and it was not clear which adverse event was related to which one of the implants.

Patients received series of injections, and not only was the duration between the injection not mentioned, but it wasn't mentioned that the adverse events occurred after which one of the injections in the series.

And also like other MDRs, direct association of the adverse events with the product inject is not identified in many of the reports, and

different reporters, as I mentioned, use different terminology to describe the site of injection and the patient problem.

This slide shows the sites of injection. 536 reports mention the site of injection and the first one is nasolabial, 191, and lips category included lips in -- order and vertical lip line. Out of 145 reports, 141 was lips.

And the next category is the periorbital. I included eye lifts and under eyes and -- 78 reports, marionette line around mouth -- fine line were all categorized in periorbital with 76, and forehead 79 and it includes -- crease -- lines -- cheeks and chin and nose didn't have subcategories and other categories are different sites of injections that didn't have reports of more than 5. So I lumped them together, hands four reports, earlobe two reports, and forearm, neck, and foot each had one report.

Before I go further, I wanted to ask you to look at these sites of injections that are other than nasolabial that was indicated for most of these dermal implants. For example, lips, for example, the cheeks, chin, nose, they're not all indicated.

For cheeks, we have two products that are

approved for HIV patients, lipoatrophy, but interestingly, 47 cheeks adverse events, only 5 patients were HIV positive and the rest were cosmetic.

This slide shows the injuries, and 823 injuries reported, we had and again 11 categories of injuries, the main one, swelling, simply swelling is 334 reports, and the next one is inflammation, inflammatory reaction. I included the aforementioned -- formation, nodule formation, granuloma -- cold sores, herpes, and arthritis flare-up all in this bundle, and the most reports were related to nodule formation and granuloma.

The next category is erythema and redness, 275 reports, and the next one is allergy group, allergic reaction, hypersensitivity, anaphylactic shock were among this group, and the next one is vascular events -- infection, infection, abscess, cellulitis, postulates -- conjunctivitis had 150 reports.

Vascular events were the ones that had bruising, bleeding, hemato non-necrosis (ph.), scars, blanching, discoloration of skin, 153 reports.

Pain of different sorts 140, and there were unknown masses that caused lumps and bumps, cysts and

blisters and -- 44. Numbness and palsy, we have 15 reports. They included lots of patient palsy, eyelid and lip palsy.

Migration with 13 reports, just simply said that the product moved from the site of injection to other site. And this other category again I lumped in the reports that had less than 10 reports, blurred vision, disfigurement, over correction, retain foreign body, fainting, tear duct obstruction and soreness, heart attack for one patient were among these other ones.

Treatment of adverse events, 638 of these injury reports specified type of treatment, but all of them because they were injury reports, they all have to be treated. And their treatment was either a medication or surgical, and medication was therapy with a steroid from topical ointment, sterile ointment to taking oral doses and interlesion injections, antibiotic, or IV. Surgical treatments were reported in 94 patients, and only 48 of them had a combination where they both were treated with medication and surgical treatment, and the surgical procedures ranged from incision and drainage of abscess to debridement and excision of nodules and granulomas and biopsy. Also 19 of these patients

were admitted to ER for anaphylactic shock or severe edema of tongue and throat, patient couldn't breathe, and 12 of them were hospitalized because they needed extended IV therapy or close monitoring. Three patients were monitored in the office for extended period of time. Now, these were all injury reports.

The malfunction reports are those that do not specify any injury as a result of dermal implants. Most of them were related to injection tools, syringe luer lock problem, needle disengagement, and syringe breakage.

Other events are the ones that are not reported injury or malfunction. They were mostly from voluntary reporters who had general complaints or physicians telling FDA to do something about this product, and because there are several adverse events, serious adverse events, patients who complained about the product wasn't effective or the manufacturer is not telling them truth and things like that. Only one reported that injector was exposed to HIV patient's blood and body fluid during the injection.

Now, summary of the analysis is that first of all, the site of objection as was mentioned, most of these are other than nasolabial folds that

indicated for these products. Then compared to the labeling of these products that we expect some of the minor adverse events such as swelling -- and that are supposed to appear in short term after a few hours or a couple of days after injection, and immediately we see serious adverse events, we see the ones that are not expected as in label. We see and they stay for a long period of time, and we see delayed onset, from weeks to months, and I've even had reports that has specified two years and more than that in some of the procedures.

The procedure condition, and I'm so glad that I heard from our colleagues from professional associations, untrained injectors are reflected in the MDRs. These injections are done in massage parlors and spa clubs and places like that, and we are seeing that non-healthcare facilities are doing this and untrained injectors are doing it.

And my questions, MDR related questions to the Panel is, first of all, do we need labeling modification? Do we need to include delayed onset and prolonged duration of adverse events in the labeling? Do we need adverse events that we did not observe in the clinical studies?

Second question is how should we be

tolerant about expecting severe adverse events in healthy individual? We in FDA checked the safety and effectiveness of the products for treatment of disease, and the ratio of risk and benefit should be different in healthy individuals. So we want to see what the Panel thinks on how tolerant we should be about these adverse events since the subjects are healthy individuals.

And then lastly, what's the best effective communication to inform the physicians about these adverse events, and I'm again happy that Congress already addressed this. Thank you very much.

DR. DANG: Does the Panel have any questions for Dr. Mirsaidi?

DR. LoCICERO: Since we have another presentation, let's have all the presentations and then the questions.

DR. DANG: Okay. Our next presenter is Azadeh Shoaibi. She is an epidemiologist in the Office of Surveillance and Biometrics. She'll be presenting on post-approval study data on soft tissue dermal fillers studied in Fitzpatrick skin IV-VI population.

DR. SHOAIBI: Good morning. This is an outline of what I will be discussing this morning. I

will be very shortly talking about post-approval studies program transformation, about the devices with post-approval studies for Fitzpatrick skin types IV-VI population, give a summary of the post-approval studies, talk about the prevalence of the dermal fillers used in Fitzpatrick skin types IV-VI population, and also give some evidence from the literature.

As you are aware, the post-approval studies program has undergone major changes in the past few years. The program was transferred to the Office of Surveillance and Biometrics from the Office of Device Evaluation in two phases. The first phase occurred in January of 2005 and the second phase in April of 2007.

The major goals of post-approval studies program transformation are to enhance scientific rigor of post-approval studies, to establish and maintain accountability for the post-approval studies commitments, to build information management system for these studies, to link postmarket knowledge to premarket device evaluation, and to increase transparency with the public.

The program transformation has resulted in major changes in the post-approval studies that CDRH

requires.

We update and track the status of ongoing post-approval studies on a regular basis, and this information is available to the public. This is a snapshot of the CDRH post-approval studies website. All the ongoing studies are listed on the website and their status is specified.

It has been established that ethnic groups differ in their facial characteristics with respect to both color and underlying structural or architectural differences. Both Asian skin and darker skin types have a higher probability of certain adverse events such as keloid formation, pigmentary changes, and hypertrophic scarring in response to insult, injury, or other modifications.

FDA has issued guidance documents for the collection or race and ethnicity data. One of these guidance documents is FDA Guidance for Industry Collection of Race and Ethnicity Data in clinical trials released in September of 2005. This guidance document states that for devices in which race and ethnicity data are relevant to determining the safety and effectiveness of the device, FDA encourages sponsors to collect race and ethnicity data.

As you are familiar with the Fitzpatrick

skin type scale, it has six categories. A category or type I includes lightest skin color and category or type VI includes the darkest skin color.

FDA has approved eight implantable soft-tissue dermal fillers for the correction of facial wrinkles and folds that required a post-approval study in the population with Fitzpatrick skin types IV-VI since 2003.

I'd like to emphasize that these eight devices are not the only ones that FDA has approved for the correction of facial wrinkles and folds, but these are the ones that required a post-approval study in the Fitzpatrick IV-VI population. Two of these devices have ongoing post-approval studies. So data are not available to us to present here today, but six of these devices have had three post-approval studies already completed and the results are available. So I will describe these studies later.

Three of these eight devices were referred to the General and Plastic Surgery Devices Advisory Panel for their premarket evaluation. The Panel's concern was the safety of these devices in people with Fitzpatrick skin types IV-VI since this population was underrepresented in the premarket studies. So the Panel recommended that sponsors

conduct a post-approval study to determine if the device was safe for use in persons of color.

The major components of these devices approved with a post-approval study for Fitzpatrick skin types IV-VI population included porcine collagen gel, hyaluronan from *Streptococcus equi*, synthetic calcium hydroxylapatite suspended in a gel carrier, cross-linked hyaluronan from an avian or bacterial source, hyaluronic acid from bacterial source. And the three devices, the last three that show in red, these are the major components that constitute the major components of the devices whose post-approval studies have been completed, and I will describe them later.

So from now on, I will focus on these three post-approval studies that have been completed.

So the objective of the post-approval studies was to evaluate the safety of the devices in the population with Fitzpatrick skin types IV-VI particularly with respect to certain adverse events including keloid information, pigmentation changes and hypertrophic scarring.

Although evaluation of effectiveness was not specified in the objective of these studies, it should be noted that evaluation of safety without

effectiveness in general and for these devices in particular, is limited.

So now I would like to present some information about the design of these three studies. So here each column represents one of these three studies, and they are not in any particular order.

The study population for all of these studies included Fitzpatrick skin types IV-VI, and none of these studies had a control or comparison group. The follow-up period for all three studies was 24 weeks after the injection.

So the first column represents one of these studies. The sample size included 100 patients, one device was evaluated, and the injection skin was one device injected into both nasolabial folds of all the subjects. All subjects received one injection into the nasolabial folds, and the study visits occurred at 12 and 24 weeks. Patients were not provided with a diary to record their adverse events for the first two weeks after the injection, and effectiveness data was not collected.

The second column here represents another study with a sample size of 119 patients. Three similar devices with the same major component from the same family of devices were evaluated in this

study. Each subject was randomized to receive one device in both nasolabial folds. All subjects received one injection into the nasolabial folds, and the study visits occurred at 2, 4, 12 and 24 weeks. No diaries were provided, and effectiveness data was not collected.

The third column represents another study with a sample size of 150 subjects. Two similar devices from the same family of devices with the same major component were evaluated in this study. And the design was a split face. Each side of the face was randomized to receive on device. Now, in this study, 49 percent of subjects received one injection and 51 percent of subjects received two injections into nasolabial folds and oral commissures, and the study visits occurred at 3 days, 2, 6, 12 and 24 weeks after injection. Patient diaries were provided to the patients to record their adverse events for the first two weeks after injection, after each injection and effectiveness data was collected.

Now, this table shows the frequency of primary adverse events that were reported in these three post-approval studies.

The primary adverse events included keloid formation, hyperpigmentation, hypopigmentation,

hypertrophic scarring and nodule or mass formation.

None of these studies reported any keloid formations. Hyperpigmentation was one case was reported by one study, and it occurred on the lips, but it was reported as not related to the device or procedure. Another study reported three cases of hyperpigmentation and they were detected -- I'm sorry. I have to correct myself here. These occurred on the lips. They were reported as not related to the device or procedure, and they were detected at the three-month visit and lasted for 159 days.

Now, the other study reported three cases of hyperpigmentation, and they were reported at the three-month visit, and they were resolved three months after using a bleaching agent.

Another study reported 17 cases of hyperpigmentation that were related to the device or procedure and 5 additional cases that were not reported as related to the device or procedure, 1 of which occurred on the lips.

For hypopigmentation, one of the studies reported one case related to the device or procedure and two additional cases not related to the device or procedure.

Hypertrophic scarring, one case was reported by one study, reported as not related to the device or procedure.

And for nodule or mass formation, nine cases were reported with a duration of 70 to 85 days, and one by another study was also reported.

Now, for adverse events reported with a frequency of 0, based on the statistical rule of 3s, the 95 percent upper bound of the rate of occurrence can be assumed. So the rate of occurrence for such adverse events in this case, in these studies, is about two to three percent.

Now, this table shows the frequency of the same primary adverse events. However, these adverse events occurred in the premarket studies for the same devices. So four premarket studies for these devices were conducted, and one study reported one hypopigmentation case and one study reported one nodule or mass formation. However, I would like to draw your attention to the proportion of patients in the premarket study that had a Fitzpatrick skin type IV-VI. One of the premarket studies had 13 percent of this type, two others had 20 percent each, and one other had 11 percent.

Now, I would like to remind you that the

sample size for these studies, the premarket studies was not in any particular order, 117, 261, 283 and 138.

Now, I would like to refer to other adverse events reported in the post-approval studies and premarket studies, and by other adverse events, I am referring to adverse events other than the primary adverse events that I just discussed in the past two slides, and these adverse events are including, but not limited to, edema, erythema, pain, pruritus, tenderness, ecchymosis, et cetera.

Although these sample sizes were comparable, the frequency of reported other adverse events in the post-approval studies was much lower than that in the premarket studies for the same device. The difference can be partially attributed to the differences in the study design between premarket and post-approval studies and design limitations of the post-approval studies.

However, please note that the direct comparison between premarket and post-approval studies may not be appropriate or relevant because of the differences in the study designs and study populations.

Now, I would like to draw your attention to

the limitations of these three post-approval studies that we just discussed. We have to evaluate these studies and draw conclusions from their results in the context of their design limitations.

So these studies were not powered to detect the low incidence of some of the primary adverse events such as keloid information or hypertrophic scarring. Two of these studies evaluated more than one device. So their power of detection of these low incidences was even more reduced.

The achievement of optimal cosmetic results was not evaluated in two of these studies. These studies did not collect any effectiveness data, and evaluation of safety without effectiveness for these devices is limited.

Also the way these devices were used in the post-approval studies is not the same way that they were used in the premarket study or the same as the instructions for use in the approved label, and the reason is that two of these devices only offered one injection to all of the subjects throughout the study whereas in premarket studies for the same devices, two or three injections were applied to a large proportion of subjects. So the application of these devices in the post-approval studies does not

represent the real world use of these devices.

None of these studies had a control or comparison group. In two studies, because data for achievement of optimal cosmetic results were not collected, subjects were not even compared to themselves pre and post-injection. In other words, between subject or within subject comparison were not made.

Two of these studies were not blinded at all. So subject and investigator bias cannot be ruled out.

Two studies did not distribute a diary to the subjects for the collection of adverse events during at least the first two weeks after the injection, and in one of these studies, the first study visit occurred three months after the injection. Therefore, there is a potential for underreporting of the adverse events.

Some primarily adverse events in this population, Fitzpatrick skin types IV-VI develop a long time after the injection. So it's unclear whether the follow-up period in the post-approval studies, which was mainly 24 weeks after injection, was long enough to detect these primary adverse events.

So, in general, these studies, these three post-approval studies were descriptive, they carry certain systematic error bias, and the generalizability of their findings is limited.

Now, I would like to shortly talk about the use of the soft-tissue dermal fillers --

DR. LoCICERO: I'm sorry. I have to -- would you please go to your summary slides? You're burning up our time.

MS. SHOAIBI: Okay. I will try to be very -- this is very important information I would like to present please.

DR. LoCICERO: Go to your summary slides.

MS. SHOAIBI: Actually, I would prefer to present the next two slides instead of the summary slides.

DR. LoCICERO: Okay.

MS. SHOAIBI: I would like to talk about the use of the soft-tissue dermal fillers in the non-Caucasian population. The American Society of Plastic Surgeons in 2007 Cosmetic Demographics reported that among aesthetic procedures, injectable fillers are one of the three most commonly requested and minimally invasive procedures among African-Americans, Asian-Americans and Hispanics.

A study that utilized -- what is the verdict? Can I continue until the end or just two slides?

Okay. I would like to go back to the previous slide.

The American Society of Plastic Surgeons in 2007 Cosmetic Demographics reported that among aesthetic procedures, injectable fillers are one of the three most commonly requested and minimally invasive procedures among African-Americans, Asian-Americans and Hispanics.

A study that utilized the data from the National Ambulatory Medical Care Survey reported that from 1995 to 2003, soft tissue dermal fillers constituted over 18 percent or 2.5 million procedures of office-based aesthetic procedure visits. Ninety percent of office-based aesthetic procedures were performed on white patients and ten percent on non-white patients.

This study also reported that application of soft tissue dermal fillers was the most common procedure among non-white subjects which constituted 27 percent of office-based aesthetic procedures among non-white subjects, and it was the second most common procedure among white subjects which constituted 17

percent of office-based aesthetic procedures among white subjects.

Also the study reported that among office-based aesthetic procedures, soft tissue dermal fillers constituted 10 visits per 1,000 white subjects and 8 visits per 1,000 non-white subjects.

So these provide evidence that dermal fillers are not just used by the Caucasian population but also by the non-Caucasian populations and that among the users of the soft tissue dermal fillers, the non-Caucasian populations are fairly large.

So in order to understand what is available in the literature, in terms of the safety and effectiveness of dermal fillers, in the Fitzpatrick skin types IV-VI, we performed a literature search.

A survey of the literature did not provide much evidence for the evaluation of safety and effectiveness of soft tissue dermal fillers in the population with Fitzpatrick skin types IV-VI. Particularly we did not find studies that evaluated these devices in this population, and the statistics for the incidence or prevalence of primary adverse events related to the use of dermal fillers in this population were not available.

So, in summary, because of study design

limitations, the results of these post-approval studies may be difficult to interpret. The literature does not provide much evidence that these devices have been evaluated in the population with Fitzpatrick skin types IV-VI. Studies that evidence the safety and effectiveness of devices should be representative of the population that utilizes the device. Current statistics provide evidence that most use of dermal fillers is seen in the Caucasian population. However, non-Caucasian populations represent a fairly significant proportion of the population that utilizes soft tissue dermal fillers.

Thank you very much. Any questions?

DR. LoCICERO: Thank you.

DR. DANG: That concludes the FDA presentations. I don't know if the Panel wants to ask questions to the presenters or to move forward with a listing of the Panel questions.

DR. LoCICERO: Are there from the Panel for the FDA? Dr. Olding first and then Dr. Bigby.

DR. OLDING: To the first presenter, I have a question about the medical device reporting. You indicated that 95 percent of that was from manufacturers.

MS. MIRSAIDI: Yes.

DR. OLDING: That's because they're obliged to report those.

MS. MIRSAIDI: Yes, mandatory reporters.

DR. OLDING: Yes, and yet we know that the vast majority of the injectable minor complications are probably not reported, or at least that's the impression one gets when there's only 5 percent are from people who are using and actually reporting them.

And I presume that this is a problem that's not just with fillers but across the FDA in general.

Have you all discussed how you might remedy that? You're asking us, but I think we need to ask you as well because you probably have discussed this and have more experience with it even than us?

MS. MIRSAIDI: Well, we offer all kinds of reporting systems, and we advertise our websites and -- for voluntary reporters. We have started MedSun hospitals network, and all we have done recently has been just for getting more information from voluntary reporters. We follow-up with manufacturers all the time when we receive, of course, and asking them to report everything they have received, check their complaints and records when inspection is going on. There's several different ways, but I guess that's

all we get.

DR. OLDING: And one more question. Do you have conversations or dialogue with, for example, in the ASPS, the tracking system, the top system, do you have a way to input that currently?

MS. MIRSAIDI: Not currently, but I believe that's what we are going to do in the future.

DR. LoCICERO: Dr. Bigby.

DR. BIGBY: I have a question for both of the speakers. The first is to Dr. Mirsaidi. Just sort of counting adverse reports doesn't really give you a sense of frequency. One way that you might be able to detect a signal is to look at the rate of reporting for injectables versus the totality of reports. Do you have any sense of what proportion of the report MedWatch fillers represent, and is it much higher than other drugs and devices?

MS. MIRSAIDI: I don't have answer to that question.

DR. BIGBY: Okay.

MS. MIRSAIDI: I don't know what others would be.

DR. BIGBY: Okay. I mean it might be helpful for you to know that if this is a signal that's out of proportion to other things, to

MedWatch, it might be important.

MS. MIRSAIDI: I will mention that we have a lot of biased information and we might get --

DR. BIGBY: Nonetheless, it might be useful. So, okay.

MS. MIRSAIDI: Okay. And for Dr. Shoaibi, you mentioned why you don't want to compare what happened in types IV-VI to those in types I-III, but you don't give the comparison. Do you have it?

MS. SHOAIBI: What I presented here is the comparison between premarket and postmarket studies in terms of the primary adverse events. And again as I mentioned, the post-approval studies, the entire population, 100 percent, for all studies was Fitzpatrick IV-VI. But for the premarket studies, the proportion of Fitzpatrick IV-VI ranged between 11 and 20 percent. So we did compare, if I can go back to my slides.

This table shows the primary adverse events listed here for the post-approval studies. You see a range. For keloid formation, we didn't have any reports other than we had some reports for other adverse events. This population for all three studies is Fitzpatrick skin types IV-VI only. However, when we go to this table, these are four

studies in similar devices or equivalent devices, premarket studies for the premarket evaluation and the proportion of the Fitzpatrick skin types IV-VI in these studies ranges between 11 and 20 percent. And we have only for these particular post-approval studies -- for these particular adverse events, we only have two reports.

We have looked up the data for other adverse events, not including these primary adverse events, and similarly, we see a much smaller frequency of reported adverse events for other adverse events in post-approval studies compared to the premarket studies. And as I mentioned before, to some extent this could be due to the differences in the design of the studies. Premarket studies, all of them were randomized. The post-approval study, not all of them were randomized. The premarket studies with a different population, of course. We're talking about two different populations here.

In the post-approval studies, two of the studies only offered one injection to all of the subjects, and diaries were not provided in two of the studies. So these are limitations of the post-approval studies that would impact on the reporting of adverse events. So that could be one reason why

post-approval studies reported smaller frequency of adverse events. Primary, well, not primary but other adverse events in general. I don't know if I answered your question.

DR. BIGBY: You did.

DR. BURKE: Can I ask one question? The premarket studies had how many patients? And also, what was the duration of the study for each? In other words, did the study go, you know, for three months, six months, to compare those two slides?

MS. SHOAIBI: Okay. I would like to mention something that we are not trying to specifically identify any specific devices for particular studies for devices. So I would like to keep the data sort of anonymous, as anonymous as possible as I have presented.

For these 4 premarket studies, the sample sizes were 117, 261, 283 and 138, in no particular order. In terms of the duration of the premarket studies, if you give me a second, I can look that up. Two of the studies followed patients for 24 weeks. One study followed patients for 12 weeks, and one study followed patients for 52 weeks. So it ranged between 12 weeks and 52 weeks. These are all premarket studies that I'm referring to.

DR. BURKE: And then the post-market.

MS. SHOAIBI: And the post-market, the duration for all of the studies was 24 weeks, that's 3 studies, and the sample sizes were 100, 119 and 150.

DR. LoCICERO: Dr. Newburger.

DR. NEWBURGER: I have questions for both speakers. Ms. Shoaibi, I'd like to first start, you said that you lumped together these different devices in order not to identify any particular product, and I question --

MS. SHOAIBI: I'm sorry. I would like to correct that. We did not lump them together.

DR. NEWBURGER: Okay.

MS. SHOAIBI: We are presenting the studies anonymously, not with respect to what device the study evaluated. However, when I say that, for example, the second column or third column from the left evaluated three devices, these are three devices with the same major component and from the same family of devices, and this constituted the post-approval study for that family of devices in the Fitzpatrick skin types IV-VI. So the data here presented as each study was conducted.

DR. NEWBURGER: I understand that, but what

my comment is, is on one of your primary adverse event post-approval slides, which has PAS A, B and C, this slide, I don't know. You have a large difference in nodule or mass formation, okay. Now, it's important for me to know if that is the calcium hydroxylapatite product or if it's the hyaluronan because I don't think it's fair across the board to make any conclusions regarding Fitzpatrick types IV, V, VI, when you don't know the mechanism of action in the skin of that one product whereas with the hyaluronans because they've been studied much more effectively and we have a lot more information, but we can be fairly certain that the mechanism of action is not the same. You can't really make those conclusions.

So I think that perhaps what you want to be doing is setting up a standard protocol whereby these parameters or patient diaries, et cetera, would be followed in Fitz types IV-VI but then adjust the duration of the study depending on what seems to be the mechanism of action and the duration of action, how it's metabolized in the individual, because that would make a tremendous difference.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: That actually is the types

of questions that we were saving for the afternoon session. We're basically presenting what we have done and not necessarily what we would potentially like to have.

DR. NEWBURGER: Thank you. I do understand that. I'm just trying to say that these data are very difficult for me to read and make any --

MR. MELKERSON: Understood, and I apologize for the difficulties, but in terms of what the plan to do in the future for these type of products is, as we get the completion of those studies, give you a complete detail for each particular manufacturer but that would require us to give the manufacturer's previous notice that this is -- we're taking you to Panel and you can present your data as you analyzed it versus our analyst. This general topics meeting was intended to say here's what we've been doing. Is this going in the right direction? Yes or no. I know it's a little out of -- disconcerting, but that's currently where we're having ourselves ask questions of our post-approval study group, help identify those issues.

DR. NEWBURGER: I withdraw my comment. Then I have a question for Ms. Mirsaidi. What mechanism do you have to compel the manufacturer to