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Quick Pulse

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FDA Panel Recommends New Labels and More Studies on Dermal Fillers and Efficacy Endpoints for Expanded Indications for Energy Delivery Devices

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The FDA's General and Plastic Surgery Devices Advisory Committee spent the first day discussing label revision for dermal fillers. The panel had significant concern about the safety of dermal fillers, especially the new, longer-lasting fillers, and agreed that labeling should be changed to reflect the types of adverse events found in postmarket studies, that longer studies are needed for longer-lasting fillers, and new indications will require clinical trials.

On the second day, the panel discussed energy delivery devices for dermatology and aesthetic indications, agreeing that there is a need for scientific endpoints when companies want to expand indications. They said that patient satisfaction is an important measure, but quantitative data are needed. The panel had a difficult time making generalized recommendations on efficacy evaluations but agreed that efficacy measurements will differ with each device. The panel agreed that a measure of efficacy should be met, but they could not agree on what that might be for any specific indication. An unspoken theme underlying the discussion was a worry by some panel members that some of the devices simply do not work. The panel also was concerned about safety, though members were unable to come up with any specific recommendations.

Day 1: Dermal Fillers

The use of dermal fillers has expanded far beyond nasolabial folds, to lip and chin augmentation and general volumizing of the face (cheeks), hands, and other body areas. The FDA received 930 reports of adverse events due to dermal fillers between 2003 and 2008, 739 of which were in the U.S. The problems included known complications, such as inflammation and minor swelling. However, some of the problems were more serious, including facial palsy, numbness, bleeding, disfigurement, and rare but life-threatening events such as severe allergic reactions and anaphylactic shock. Because of this, the panel said that new safety studies will have to be done for new indications. In addition, longer studies will be needed for longer-lasting fillers.

The panel generally agreed that:

- Labeling should be modified to include adverse events not observed during clinical trials but observed in postmarket adverse event reporting.
- The FDA should have a lower tolerance for adverse events in dermal fillers for healthy patients compared to other devices for sick patients.

- The use of fillers for augmenting tissue volume and re-contouring tissue cannot be an extension of filler use for wrinkle correction and indications such as nasolabial folds.
- Postmarketing information should be widely disseminated by a variety of sources, including industry organizations, the FDA, and physicians.
- Fitzpatrick scale scores I-II and IV-VI should not be considered separate populations, with the potential to exhibit different safety profiles. Instead, panel members said that there is overlap among the scale scores. They also said that it would be misleading to use skin types to predict response.
- For new indications, new wrinkle severity/global aesthetic improvement scales and patient satisfaction questionnaires will be needed.
- Longer studies should be required for clinical trials, especially for longer-lasting dermal fillers. Some ongoing filler trials may have to be extended.
- The panel said that choice of control will be different for each tested device.

There were no formal votes (or even a show of hands) on any of the 13 questions the FDA posed to the panel. Often, the panel chair, Dr. Joseph LoCicero III, chief of surgical oncology at Maimonides Medical Center in Brooklyn NY, would moderate a discussion and then ask the FDA if the question was answered satisfactorily. In part, the panel felt it didn't have enough information about the studies presented at the meeting. Panel members were disappointed and displeased with the small numbers of patients in the studies and with how the FDA presented the postmarket study data.

Regarding **trial design**, the panel said that efficacy will largely be patient-driven and that new patient questionnaires are needed to show satisfaction and improved quality of life. Some of the physicians organizations are working on questionnaires that will focus on the face and other areas where dermal fillers might be used, and panel members said that they will be helpful. Panel members said that masked evaluation is preferred to non-masked evaluation (to try to eliminate bias) and both live and photographic evaluations are valuable when it comes to trial endpoints. The panel also agreed that current exclusion of patients who have had recent cosmetic procedures from clinical trials is not realistic, as many patients have multiple cosmetic procedures, and even use other products (for example, a dermal filler and Botox) simultaneously.

When it came to **post-approval studies**, the panel was disappointed in what it saw. Members said they could not reach any firm conclusions from the data, which did not disclose which devices (products) had more adverse events compared to others. Panel members were stymied, saying that trial designs would have to be different for each product. At the end of the day, an exasperated panel chair said, "Come on, the FDA has been beaten up on postmarket studies, and we have no recommendations."

Panel members did agree that **safety** should be the most important endpoint, and that long-term studies are necessary for non-absorbable fillers. They said that efforts should be made to make pre-market studies as thorough as possible, so that postmarket studies would not have to address huge problems. The panel decided that a consensus panel made up of industry, doctors, academia, and professional groups would be useful in making study guidelines.

As for **clinical study design** for new indications, the panel agreed that fillers for new indications such as tissue volume, lip augmentation, chin and nose contouring, under-eye injection, and hand volume restoration cannot be considered as an extension of filler use for wrinkle correction. Panel members said that the only area of the face that is similar to nasolabial

FDA-Approved Dermal Fillers

Company	Product	Key component	Use
Allergan	Zyderm	N/A	Contour deformities of the dermis in non-weight-bearing areas
Allergan	Zyplast	N/A	Contour deficiencies of soft tissue
Allergan	Juvederm	Hyaluronic acid from bacterial source	Moderate-to-severe facial wrinkles and folds
Allergan	Cosmoderm and Cosmoplast	N/A	Soft tissue contour deficiencies, such as wrinkles and acne scars
Anika Therapeutics	Elevess	Hyaluronan from *streptococcus equi*	Moderate-to-severe facial wrinkles and folds
Artes Medical	ArteFill/Artecoll	Polymethylmethacrylate microspheres suspended in a carrier gel	Nasolabial folds
BioForm Medical	Radiesse	N/A	Severe wrinkles and folds, such as nasolabial folds, as well as lipoatrophy
Colbar Lifesciences/ Johnson & Johnson	Evolence	Porcine collagen gel	Moderate-to-deep facial wrinkles and folds
Genzyme	Hylaform and Hylaform Plus	Cross-linked hyaluronan from *streptococcus equi*	Facial wrinkles and folds, such as nasolabial folds
Medicis	Restylane and Perlane	Cross-linked hyaluronan from an avian or bacterial source	Moderate-to-severe facial wrinkles and folds
Sanofi-Aventis	Sculptra	N/A	Lipoatrophy

folds may be around the mouth, but not enough is known about the other areas of the face and body where fillers may be used. For those new areas, there will be different safety and efficacy endpoints. The FDA tried to press the panel on this question, asking about specific areas such as lip augmentation and hand restoration and whether there should be a safety endpoint that focuses on impact on nerves and possible loss of function in those areas. The panel generally thought that would be a good idea.

Finally, the panel discussed trial **controls**. Panel members agreed that sham/saline as control would not work, because it would be too obvious. Michael Halpin, vice president of Regulatory Affairs at Genzyme and the industry representative, suggested using a subject's baseline as control, and the panel agreed that that would work in some cases, but not all. No satisfactory control was agreed upon.

BACKGROUND

Nasolabial folds are considered representative of moderate-to-severe facial wrinkles and folds, and study data were used to support approved indications of dermal fillers. However, fillers are increasingly used to augment and contour tissues, and the FDA expects that manufacturers will request new indications.

All dermal fillers are contraindicated for patients with known sensitivity to the material, history of severe allergy, anaphylaxis, or bleeding disorders. Current warnings include:

- Avoid injection into blood vessels as vascular occlusion (and possible subsequent tissue necrosis) may occur.
- Injection should be deferred until infection or inflammation has been controlled or resolved.
- Injection into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- The safety and effectiveness of device injection for lip augmentation has not been established.
- The safety in patients susceptible to keloid formation, hyperpigmentation, and hypertrophic scarring has not been established.
- Long-term safety and effectiveness beyond duration of clinical safety have not been investigated.

PUBLIC WITNESSES

Dermatologist Dr. Kelley Redbord, representing the American Academy of Dermatology (AAD), told the panel that dermal fillers are ***important for things other than purely cosmetic uses, including scarring***. The AAD urged the panel to make sure that professionals have the right training and are adequately monitored in order to prevent complications. Dr. Redbord, who has expertise with Sculptra, said that the incidence of complications is very low when implementation is monitored carefully.

Christopher Marmo, senior vice president for global R&D at Allergan, said that his company's product, ***Juvederm, is very safe***, pure, and biocompatible. Juvederm uses a cross-linked hyaluronic acid (HA) filler and is not animal-derived. He said the product is manufactured "using strict controls and multiple steps to ensure purity." Juvederm has had a C.E. Mark since 2000 and is approved in almost 50 countries. Since FDA approval in June 2006, more than a million syringes of Juvederm have been used. In the pivotal study, 160 of 439 subjects included 60 patients with Fitzpatrick skin type IV-VI, and the FDA did not require the company to do any postmarketing trials. Marmo said, "Clinical study results showed no serious adverse events related to Juvederm treatment, and most side effects were mild or moderate in nature, and their duration was short-lasting (7 days or less)." Most common side effects were redness, pain, and swelling. He concluded that Juvederm has a "very impressive safety profile and presents minimal risk to the patient."

Dr. Alan Gold, a plastic surgeon in private practice in Great Neck NY and president of the American Society of Aesthetic Plastic Surgery (ASAPS), said that surgeons are concerned with safety and efficacy, "It is all about the patient." He said that the ASAPS ***wants to eliminate the delivery of some products (devices) by unqualified people*** and to promote only the use of FDA-approved, appropriately-obtained, and appropriately-administered products. Dr. Gold said that the ASAPS wants to work with the FDA on outcome studies to measure quality of life improvement, patient satisfaction, etc. In response to one of the FDA's questions to the panel, he offered his organization's member newsletter as well as its website and coalition partners' websites as a way for the FDA to efficiently communicate with physicians about adverse events, etc. He also proposed an FDA section on an as-needed basis in the ***Aesthetic Society Journal***. He said that FDA collection and publication of postmarket data would be unfiltered without industry bias.

Dr. Richard D'Amico, a plastic surgeon in Englewood NJ and immediate past president of the American Society of Plastic Surgeons (ASPS), said that minimally invasive cosmetic procedures rose to nearly 10 million procedures in 2007. Demand is increasing, and HA procedures jumped from the fifth most popular procedure in 2007 to second place, "We believe the data also represent an obligation for continued vigilance...ASPS believes that it is critically important for patients to consult ***qualified physicians***…We believe a coordinated cross-disciplinary (approach) is absolutely needed."

Dr. D'Amico also suggested a ***multispecialty global consensus conference*** charged with standardizing criteria for measuring safety and effectiveness for facial aesthetics

cosmetic devices, particularly in the long term, "Developing widespread consensus on measurement tools and methods… results in the development of a coordinated effort across the field to facilitate meaningful study design, data collection, measurement, and analysis…Postmarket surveillance studies are a key element…Plastic surgeons are committed to continued quality learning and improvement."

Dr. Arnold William Klein, a dermatologist at UCLA and the self-professed inventor of lip augmentation, told the panel that fillers must be pure, must not cause inflammation, and should not be synthetic, "You don't want anything synthetic under the skin…And you want the integrity of the scientific data behind you." He said that one big problem is that injectors don't know ***how to inject properly***, "The number one site of injection is the lip (about which he wrote a textbook that pointed out problems with lumps)…If you have that many problems in injecting, that means you don't know how to inject. You have to have people who know what they're doing. I call it the 'invasion of the filler snatchers.' Many individuals are entering the field of soft tissue augmentation."

Dr. Klein said that there are long-term problems with permanent fillers, including facial contours changing over time and permanent fillers becoming more visible, creating an unnatural look. He claimed physicians are not reporting adverse events with fillers, adding, "Basically, the panel has a poor understanding of the entire field of soft tissue augmentation. Product approval must go before the panel. Some fillers were approved without first going before the panel."

Dr. Klein discussed issues with some specific products:

- Artes Medical's Artecoll/ArteFill. He said there are global concerns about this product, claiming Swiss and German physicians are being told that it is "disastrous" but that this information is not being disseminated in the U.S.
- Sanofi-Aventis's Sculptra. He said that in studies in HIV patients, Sculptra caused 55% of patients to develop nodules, adding, "None of that was presented to the FDA."
- BioForm Medical's Radiesse. He said this also causes lumps under the skin, especially in the lips, "You have agents approved, and there is no idea of how they function under the skin."

Dr. Ira Lawrence of Medicis told the panel that most adverse events were local at the site of injection and short in duration. He said the company recently updated its adverse events data, "We respectfully suggest that the panel suggest similar rigor (to all fillers) because of their different aspects." On clinical study design, he said that his company would ask for new indications for additional folds and wrinkles. He said that ***dermal filler clients "want immediate action and may not be good candidates for long-term studies***…We have some concern…on the (FDA) proposal for histological-based biopsy samples…These devices are often used on the face…where a scar would pose an unacceptable risk for patients."

American Society for Dermatologic Surgery (ASDS) president Dr. Robert Weiss said that his organization's 2007 survey found that its members had performed more than a million procedures using dermal fillers. His own informal survey over the weekend before the panel meeting questioned 50 teachers of injection technique, and it showed that members feel that ***side effects were no different in all Fitzpatrick types***. The ASDS said that complications from the use of dermal fillers, while rare, are frequently caused by injection technique, and many ***complications can be prevented by proper training and screening***. Dr. Weiss added, "Stronger safeguards should be put into place…including thorough training."

Dr. Steven Fagan, **a plastic surgeon in private practice in Boca Raton FL**, said that pivotal trials for new indications should be randomized and ***include a control arm***. Products evaluated should have similar characteristics to optimize the research. He said that there may be no good controls, "Saline may be immediately or soon obvious and may raise ethical questions." He laid out an argument against using autologous fat transfer as a control, saying that ***autologous fat is not a dermal filler and should not be a control*** because of:

- Limited number of physicians performing fat injections.
- Patient enrollment difficulties.
- Sophisticated apparatus required.
- Variability of fat procurement, processing, and injection techniques.
- Introducing a second procedure to harvest fat may deter patients.
- Patients are more likely to exit the study.
- Patients could opt for off-label injection of HA fillers instead.
- Many times patients are seeking instant gratification and don't want to go through the rigors of a trial.
- There is no standard method for fat injection.

He added, "Finally, there are significant inherent variabilities in outcomes in using autologous products vs. synthetic/manufactured filling agents such as HA. The reason for failure in the former relate to many issues not associated with products such as HA, for example, what happens when someone gains a lot of weight."

Study design concerns include blinding difficulties, follow-up schedule difficulties, and injection technique differences. Some edema and morbidity also are associated with fat injections. He said, "I promise you that, using autologous fat as a comparator, you will get more adverse events. The best

control may be a non-treatment control group. Autologous fat is a suboptimal control."

Dr. Diana Zuckerman, president of the National Research Center for Women and Families and a noted women's health expert, said, "We know that some people are having serious unexpected adverse reactions. The FDA has approved these products based on small, short-term studies. So, it's not surprising that these adverse effects weren't noticed when the products were approved. The products were used primarily on white patients, and we know there can be differences due to skin type."

She admonished the FDA, "This should not be a postmarket question. ***These products should have been studied on people with diverse skin types before they were approved***, and we shouldn't be waiting until afterwards. Now, looking at them, they should have been well-designed and well-done (studies). And if the studies don't fulfill those requirements, the products should be removed from the market, or there should be large warnings about use…in people of color…It is your (the FDA's) job to see if these products are safe and effective. Since they have cosmetic benefits, not medical ones, we need to take all these reports seriously. Patients don't want to get rid of wrinkles and end up with large lumps in their face instead. The FDA has been approving these products for market based on very small, sometimes poorly designed, studies. The FDA standards have been lower than standards for lifesaving medical products when, in fact, they should be higher. The FDA should be requiring better studies since (dermal fillers) have potential for lethal, life-changing risks. Our center has received calls especially about the permanent fillers – such as Artecoll and silicone – which can have long lasting, disastrous results. I got an email from a mother whose son is hiding out in his home and who can no longer go out in public. He is growing a beard and hoping that some of the disfigurement from ArteFill will not be so noticeable if he grows a beard. Even for this patient, it's a devastating experience particularly since he blamed himself. He went in for minor wrinkles and ended up with a face that looks asymmetrical and unusually abnormal…I have heard some discussion on experiences you have had with patients. We're hearing from patients, and most of the patients we hear from have not reported their adverse events to the FDA, and their doctors haven't either."

Dr. Zuckerman said that the biggest weakness in the approval process is that the FDA relies on studies of patients treated once, twice, or three times and studied for a year or less. However, patients are using the fillers many times – every six months for some products, which haven't been studied that way. She said that the FDA's small database indicates that allergies and cosmetic problems can occur later, sometimes years later, "For permanent fillers we've heard about lumps the size of cherries and sometimes even ping pong balls, so although these products clearly have some benefits, do they outweigh the risks? And if they do for some products, do they outweigh the risks for all products? The FDA hasn't been willing to talk about postmarket problems of specific fillers, and consumers deserve to have this information. Some products don't have these adverse events, and some of them do. In the approval of these products, there has been reliance on approving the products relatively quickly and relying on postmarket studies and surveillance to find out what goes on in the real world. I've spoken with the FDA Commissioner privately and publicly and heard him state that the FDA's postmarket program does not work. The data are not automatically entered. They don't have the proper software or hardware to do that. The system is broken, and it will take years to fix it. They (the FDA) are spending millions of dollars to fix the system, but the FDA could not handle the load...So, when advisory panels like this one depend on postmarket studies or adverse event reporting, it doesn't work. It's not going to work. We have to shift responsibility for proving safety and effectiveness to the pre-market, not postmarket."

Panel questions for these speakers

Panel member Dr. Michael Bigby, a dermatologist at Harvard Medical School and Beth Israel Deaconess Medical Center, asked which physicians should be considered qualified to inject dermal fillers. Dr. D'Amico answered, "There are areas of the country, states in fact, which allow injection by non physicians – either nurses, physicians assistants, and sometimes trained technicians." He said that his organization wants a training system for all potential injectors.

Panel member Dr. Mary McGrath, a plastic surgeon from the University of California, San Francisco, asked Dr. Gold and Dr. D'Amico for their recommendations. Dr. Gold suggested a Physicians Coalition for Injectable Safety (which exists), and Dr. D'Amico suggested convening a consensus group that would specifically deal with the issues before the panel.

Dr. Rebecca Anderson, a professor of surgery, psychiatry, and epidemiology at the Medical College of Wisconsin, asked if either Dr. Gold or Dr. D'Amico had specific training plans for injectors and for off-label use. The physicians said that they did not. Dr. D'Amico commented, "We understand that initial studies have to be focused, but long-term studies can have a broader base and can incorporate the natural progression of natural science, and off-label uses are part of that process." Dr. Gold said, "Sometimes a doctor will have a brilliant idea for off-label use but won't have a database…The outreach by the FDA to get the communication out to the practicing physician of those long-term studies adverse events reports is absolutely crucial…The reporting of those adverse events is crucial for us…It is a significant issue for us in terms of off-label use."

Dr. Amy Newburger, a dermatologist from St. Luke's Roosevelt Hospital Medical Center, said that she visited the dermal filler safety website, which "is clearly sponsored by companies," adding that "it seemed there was a tremendous list of the off-label uses for these products, and it almost was

an exhortation. That would be a great place to talk about the pitfalls, but I read it as someone looking at this might say, 'Okay I might try it here because it's listed.'" Dr. Gold answered, "Absolutely, that's why I'd ask for participation from the FDA. It's a public website as well, and it's a way of trying to get reliable information out there. It's not that it's being promoted by any industry supporters...but the use off-label for almost all of the injectable products is greater than the on-label usage for the areas – the specific areas – under which it was approved. Your point is well taken, but it is the intent to incorporate into that website the adverse events."

Panel member Stephen Li PhD, president of Medical Device Testing and Innovations in Sarasota FL and an expert in the testing and research and development of biomedical materials, said, "The reporting of all types of adverse events has been a historically impossible endeavor. In orthopedic devices, far less than 1% of adverse events are reported to the FDA. Do you have some system of protocol that you can envision that would solve this problem?" Dr. Gold responded, "As part of the injectable coalition, we are developing protocols for adverse event reporting which we would encourage all the member organizations to report to their membership. We were able to witness something that we really didn't know we could develop earlier on in respect to the breast implant postmarket surveillance…Once we developed the templates for that, adverse event reporting information can be gathered. We look to do that cross-specialty." Dr. D'Amico added, "There are some social witch-hunts out there…that prevent collection of data…We can now real time monitor members' practices, and the idea as we gather the data real time as it comes in – all the data including adverse events – the accrediting body has mandatory real-time online reporting requirements for adverse events (breast implants), so we've made a lot of steps in developing a culture in our specialties to have physicians step up."

Dr. McGrath asked Dr. Fagan about saving autologous fat, who responded, "There is no approved agent for use in cheeks or lips. You'd have to use an acceptable substance, like saline, which is not regulated. Another option would be using something that would be acceptable but not approved. But if we want to stick to guidelines as having a comparator that is approved for a specific facial region, then we are at a loss. That's why we are offering the option. Saline might be the best or simplest. I still find that the problems are proximal to the syringe and have less to do with the product itself."

THE FDA PERSPECTIVE

Dr. David Krause PhD, branch chief of the FDA's Plastic and Reconstructive Surgery branch, Center for Devices and Radiological Health (CDRH), gave an update on what the FDA has done in the area of plastic surgery since the panel's last meeting in August 2006. At that meeting, the panel recommended approval (with conditions) for BioForm's PMA for Radiesse to be used for the treatment of HIV-associated lipoatrophy.

Since then, the FDA:

- Approved Medafor's Arista AH as an adjunctive absorbable hemostatic device.
- In October 2006 and 2007 PMAs were approved for Allergan's and Mentor's silicone filled breast implants.
- In December 2006 Anika Therapeutics' filler material was approved for injection into the mid to deep dermis for correction.
- In December 2006 two PMAs for BioForm's Radiesse were approved.
- In February 2007 Kamm and Associates' Histoacryl, a topical skin adhesive for skin closure, was approved.
- In June 2008 approved a PMA for Johnson & Johnson's Evolence collagen filler for wrinkles and folds.
- In May 2008 the FDA reclassified the tissue adhesive from Class 3 to Class 2.
- Gave 510(k) clearance (not approval) for Palomar's ABC Light-Based hair removal system.
- In February 2008 Light Biosciences' Gentlewaves received 510(k) clearance.
- In March 2008 the FDA gave 510(k) "substantial equivalence" for Photo Therapeutics' Omnilux New-U for peri-orbital wrinkles.
- In November 2008 the FDA cleared the Pharos Life Corps' Tanda Skincare System for mild-to-inflammatory acne.

Jiyoung Dang PhD of the FDA's Office of Device Evaluation, Division of General, Restorative, and Neurological Devices, Plastic and Reconstructive Devices branch, gave an overview of current labeling for dermal fillers. The FDA approved the first dermal filler in 1981, and the majority of dermal fillers were approved after 2000, including five approved in 2006. There was a 100% increase in dermal filler use between 2000 and 2006 and a 25% increase between 2006 and 2007. There were 587,615 procedures in 2000, 1.18 million in 2006, and 1.48 million in 2007. Indications for use:

- Injection into mid to deep dermis for the correction of moderate-to-severe wrinkles and folds.
- Correction of nasolabial folds (contraindicated for injection in areas other than nasolabial folds).
- Restoration and/or correction of signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus (HIV).

Dr. Dang listed the adverse events reported in patient diaries and case report forms, including pain, erythema, swelling,

bruising, pruritis, and induration. Adverse events lasted from a number of days from symptom outset until resolution.

Nasrin Mirsaidi RN, MSN, from the FDA's Division of Postmarket Surveillance in the Office of Surveillance and Biometrics, described the limitations of the FDA's medical device reporting (MDR) system, which is a nationwide passive surveillance system with both mandatory (manufacturers, importers, and user facilities) and voluntary (healthcare providers and consumers) reporting. Limitations include incomplete and non-validated data. Other limitations include:

- Patients received multiple injections in different sites.
- Patients received multiple brands of dermal implants.
- Patients received a series of injections.
- Direct association of the adverse events with the product is not identified in most reports.
- Different reporters used different terms for the site of injections and patients' problems.
- No incidence data, which may have incomplete numerator or lack of denominator.
- Biased information, with reporting or narrative variations.
- Uncertain causality, with lack of device failure analysis.

Some of the common adverse events that were expected to occur shortly after injection and resolve quickly actually had delayed onset and remained for a long period of time or turned into more serious problems. There were some indications that allergic reactions occurred after the second or third injection. Some reports also implied that injections were performed by untrained personnel or in settings other than health clinics or doctors' offices.

Of the 823 injuries, 638 required treatment with medication, and 94 needed surgical intervention, including opening an abscess for pus drainage, excision of nodules, and lesion biopsies. Medications ranged from topical steroid creams to multiple courses of oral antibiotics, topical steroids, anti-inflammatory or antihistamine drugs, and intra-lesion steroid injections.

Nineteen adverse events resulted in emergency room admission for severe hypersensitivity reactions, such as swollen tongue, difficulty breathing, and anaphylactic shock. Twelve patients required hospitalization for extended IV antibiotics and close monitoring. Three patients spent an "extended period of time" in the clinic. In 135 reports, no treatment of adverse events was specified.

Of the 93 so-called "malfunctions," 90 were related to syringe luer lock problems and needle disengagement. Three indicated syringe breakage. Mirsaidi said that there was no injury as a result of dermal implants; most were due to a syringe luer lock problem, and there was also needle disengagement and syringe

Dermal Filler Adverse Event Reports
(94.3% from manufacturers, 5.7% voluntary)

Measurement	2003	2004	2005	2006	2007	2008
Number of reports	216	159	136	130	160	131

Type of Adverse Events with Dermal Fillers

Type	Percentage
Death	0
Injury	88.5%
Malfunction (n=93)	10%
Other	1.5%

Dermal Filler Events by Injection Site (n=536)

Site of injection	Number of reports (n=657)
Nasolabial	191
Lips	145
Peri-orbital	78
Peri-oral	76
Forehead	79
Cheeks	47
Chin	15
Nose	16
Hand	4
Forearm	1
Earlobe	2
Nipple	1
Neck	1
Foot	1

Frequency of Adverse Events with Dermal Fillers by Event Category (n=823)

Event category	Frequency of occurrence (n=1,730)
Swelling	334
Inflammation	292 (nodule formation 163, granulomas 36, induration, papules, cold sores, herpes flare-ups, arthritis flare-ups)
Erythema	275
Allergy	230 (allergic reaction 134, hypersensitivity 79, anaphylactic shock 2, hives, itching, rash, urticaria, angioedema, and hyperpigmentation)
Infection	150 (infection, abscess, cellulitis, postulate, uveitis, conjunctivitis, pus, drainage)
Vascular events	163 Bruising, bleeding, hematoma, necrosis, scars, blanching, dehydration, ischemia)
Pain	140 (pain at injection site, muscle ache, headache)
Lumps/bumps	44
Blister/cyst	39
Numbness	15 (bumbles, parethesia, and palsy of the face, eyelid, and lips)
Migration	13
Bleeding	13
Other	22 (blurred vision 6, disfigurement 4, over-correction 4, retained foreign body 1, fainting 2, tear duct obstruction 2, heart attack 1)

indicated the wrong product was injected with no resulting adverse event, and one reported unspecified patient injury as a result of tools malfunction.

Approval of nine of the currently-approved dermal fillers carried a condition that the sponsors conduct a post-approval study (PAS) in patients with Fitzpatrick skin types IV-VI, who were under-represented in pre-market clinical studies. Post-approval studies for three fillers are still recruiting patients. Three post-approval safety studies for the other six devices were completed between 2005 and 2007, looking at specific adverse events including keloid formation, pigmentation changes, hypertrophic scarring, and hypersensitivity.

Procedure-Related Adverse Events in Completed Post-Approval Studies in Patients with Fitzpatrick IV-VI Skin Types

Adverse event	Incidence
Hypersensitivity	0
Keloid formation	0
Hypertrophic scarring	0
Hyperpigmentation	20
Hypopigmentation	1
Nodule/mass formation	10

The duration of nodule/mass formation events reported was 70-85 days. None of the studies included a control group. Subjects were followed up to six months. The FDA said that although statistics on the incidences of keloid formation, pigmentation changes, and hypertrophic scarring in people with darker skin after dermal fillers are not available, some anecdotal evidence shows that there is an incidence of keloids between 4.5% and 16%. The incidence of hypertrophic scars is possibly higher than that of keloids, but good data are lacking.

Skin types. Azade Shoaibi MS, MHS, an epidemiologist in the FDA's Office of Surveillance and Biometrics, reviewed the status of post-approval studies in the Fitzpatrick skin types IV-VI population. The CDRH Post-Approval Studies (PAS) program is an electronic system to track the progress of post-approval studies.

Asian and darker skin types have a higher probability of certain adverse events such as keloid formation, pigmentary changes, and the hypertrophic scarring in response to insult or injury. The Fitzpatrick scale is a numerical classification scheme based on tanning and burning history and physical assessment of skin pigmentation

Fitzpatrick Skin Types

Type	Description
1	Always burns, never tans
2	Always burns, slightly tans
3	Sometimes burns, always tans
4	Never burns, always tans
5	Lightly pigmented
6	Dark

The FDA encourages sponsors to collect race and ethnicity data when they are relevant to determining the safety and effectiveness of a device. All nine FDA-approved implantable soft tissue dermal fillers must conduct post-approval studies in the patient population with Fitzpatrick skin types IV-VI. PAS for three devices are ongoing, with no data yet. Three post-approval studies or six devices are completed and were referred to the General and Plastic Surgery Devices panel. The PAS looked at the likelihood of keloid formation, pigmentation changes, and hypertrophic skin changes in patients with Fitzpatrick skin types IV-VI.

PAS Fitzpatrick IV-VI – Study Design ***(no comparison group)***

Measurement	PAS 1 n=100	PAS 2 n=119	PAS 3 n=150
Number of devices evaluated	1	3	2
Injection scheme	1 device in both nasolabial folds of all patients	Each subject randomized to receive one device in both nasolabial folds	Split face design, each side of face randomized to receive one device
Number of injections	1	1	1=73 (49%) 2=77 (51%)
Injection sites	Nasolabial folds	Nasolabial folds	Nasolabial folds and oral commissures
Study visits	12 and 24 weeks	2, 4, 12, and 24 weeks	3 days; 2, 6, 12, and 24 weeks
Patient diary	No	No	Yes
Effectiveness data	No	No	Yes
Adverse events			
Keloid formation	0	0	0
Hyperpigmentation	1 *	3 **	17
Hypopigmentation	0	0	1 (2) ††
Hypertrophic scarring	0	0	0 (1) ††
Nodule/mass formation	Data not collected	9 †	1

* on the lips, reported as not related to device/procedure; detected at three-month visit, lasted for 159 days
** resolved in three months using a bleaching agent † duration 70-85 days †† reported as not related to device/procedure

PAS 3 – Other Adverse Events (Postmarket)

Adverse event	Relationship to device/procedure	
	Related	Unrelated
Bruising	23	4
Swelling	---	5
Burning	---	1
Itching	1	1
Pain	6	1
Erythema	32	---
Tenderness	8	---
Edema	8	---
Cyst on lips	---	2
Abscess	---	1
Scabbing	3	---
Other: comedones, fever, blister on lip, first degree burn, flaking	---	5

PAS 3 – Pre-Market Adverse Events (Investigator-Identified)

Adverse event	Device A n=141	Device A n=141	Device B n=142	Device B n=142
Time point post-injection	72 hours	≥2 weeks	72 hours	≥2 weeks
Ecchymosis	44	15	48	14
Edema	10	3	6	2
Erythema	5	2	3	1
Tenderness	5	1	7	0
Pain	2	0	2	1
Hyperpigmentation	1	0	0	0
Pruritus	0	0	1	1
Papule	2	1	2	2

PAS 1 – Other Adverse Events (Pre-Market and Postmarket)

Adverse event	Post-approval study n=100	Pre-market study n=117	Pre-market study n=117
Frequency of event reporting	At 3 month visit *	In diaries for first 14 days	By patients and investigators after first 14 days
Bumpiness	1	---	---
Ecchymosis	7	74	91
Edema	12	81	104
Erythema	16	78	105
Eye Sty	1	---	---
Bleeding at injection site	1	---	---
Needle jamming	1	---	---
Tenderness	2	---	---
Nodule	---	1	1
Pain	---	33	40
Pruritus	---	21	24
Other (injection sites)	---	35	52
Other (not injection sites)	2	12	---

* no adverse events reported at six-month visit

In 2007, the American Society of Plastic Surgeons said that injectable fillers are one of the three most commonly requested and minimally invasive procedures among African Americans, Asian Americans, and Hispanics. From 1995 to 2003, soft tissue fillers constituted 18.4% (more than 2.5 million procedures) of office-based cosmetic procedure visits. Although 90% of the procedures were performed on white patients and 10% on non-white patients, the most common procedure for non-whites was dermal filler injections (27%). It was the second most common procedure for white patients (17%). For these procedures, dermal fillers were the reason for 10 visits per 1,000 white patients and eight visits per 1,000 non-white patients.

There is not much literature on the safety and efficacy of dermal fillers in Fitzpatrick skin type IV-VI patients. The FDA officer concluded:

- Because of study design limitations, the results of these post-approval studies are limited and should be evaluated with caution.
- Studies are descriptive and carry certain systematic errors/ bias, and the generalizability of their findings is limited.
- Comparison of safety results between pre-market and post-approval studies for the same devices is not necessarily appropriate and relevant because of differences in study design and the difference in study population with respect to Fitzpatrick skin types.
- The application of devices in these studies does not represent the real-world use of the devices, so the validity of study results is limited.
- The literature does not provide evidence that these devices have been evaluated in the population with Fitzpatrick skin types IV-VI.
- Current statistics provide evidence that non-whites represent a larger proportion of population that uses dermal fillers, and the most common office-based non-invasive procedure in the non-white population is dermal fillers.
- Studies that evaluate the safety and effectiveness of devices should be representative of the population that utilizes the device.

Clinical design. Dr. Dang discussed clinical considerations for potential new indications for use, including fillers for tissue recontouring and volume augmentation in contrast to filling of wrinkles. She asked if the physiology of faces can be applicable to other body sites, and asked if the safety and effectiveness data that exist are representative of tissue augmentation.

Clinical study design considerations for new indications:

- Appropriate controls
- Safety and effectiveness endpoints
- Evaluation methods for effectiveness
- Short- and long-term device safety and effectiveness
- Post-approval study design considerations

The FDA expects manufacturers to submit pre-market applications for dermal fillers for:

- Lip augmentation
- Contouring of the chin
- Contouring of the nose
- Cheek augmentation
- Hand volume augmentation

However, injection other than filling wrinkles may introduce new risks due to differences in physiology of injection region, such as:

- Proximity to bone
- Proximity to nerves and vessels
- Vascular occlusion
- Thickness of dermal and sub-dermal layers
- Tolerance to swelling
- Dynamic range of motion of tissue
- Tissue function (sensory, motor, etc.)
- Device migration

Dr. Dang said that the use of the control device provides a method to study potential risks of treatment procedure independent of the study device and decreases bias. However, adequate control may not exist for all cases.

Efficacy endpoints may include adverse events, aesthetic improvement, validated assessment, frequency of filler injection for optimal and/or maintenance of correction. Safety endpoints may be specific to injection site, amount, and frequency of filler injected, effect on native tissue physiology, tissue scarring, and toxicity. Study duration could include durability of treatment and short- and long-term clinical issues, such as efficacy and safety.

Baseline safety and effectiveness data from clinical study data are needed to support pre-market approval for filling of wrinkles and folds include adverse events, aesthetic considerations for effectiveness, immune response, and inflammatory response. Controls, study endpoints, study duration, and input into clinical study designs are also important.

Dr. Jacqueline Francis, medical officer in the FDA's Division of General, Restorative, and Neurological Devices in the Office of Device Evaluation, CDRH, discussed clinical study design for pre-market approval of all dermal fillers. Current designs look at dermal fillers for: nasolabial folds, moderate-to-severe facial wrinkles, facial folds and wrinkles (nasolabial folds and oral commissures), or correction of soft tissue contour deficiencies. Current control designs include split face or standard design where one cohort of patients received control device and the other cohort received the study device. Evaluation has ranged from live assessment to photographic assessment using Modified Fitzpatrick Wrinkle Scales (MFWS) or six-point validated wrinkle severity scales. From 117 to 191 subjects were enrolled in the studies and 115 to 185 subjects completed the studies. Patients were 30- to 77-years-old, with mean ages ranging from 52-56, and female (90%-94%) and Caucasian (72%-93%).

PANEL DISCUSSION AND QUESTIONS FOR THE FDA

Before discussing the first group of FDA questions, the panel discussed the problem of the low rate of reporting, with no real resolution to the question. They agreed that they didn't have enough information on adverse events to make really informed decisions.

Fitzpatrick scale. Asked if the FDA had any comparisons of Fitzpatrick scale I-III patients compared to IV-VI patients, an FDA staffer said, "What I presented was pre-market approval studies compared to post-approval studies. For all the post-approval studies it was IV-VI. However, four pre-market studies of primary adverse events showed that the proportion of Fitzpatrick skin types IV-VI ranged from 11%-20%. We have looked at the data for other adverse events not including these primary adverse events and similarly we see a much smaller frequency of reported adverse events in post-approval studies compared to pre-market approval studies. This could be due to differences in design of the studies. Pre-market studies were randomized; not all the post-approval studies were randomized. You're talking about two different populations here. In the post-approval studies, two studies only offered one injection to all the subjects, and diaries were not provided in two of the studies. These are limitations of the studies that would impact on the reporting of adverse events. Post-approval studies recorded smaller numbers of adverse events."

Adverse events. Several panel members expressed frustration that they could not see which devices (in the postmarket studies) had more adverse events than others. This exchange resulted:

- *FDA staffer:* "We are not identifying studies for devices. We want to keep the data as anonymous as possible. For the four pre-market studies, the duration ranged from 12-52 weeks, and the postmarket studies lasted 24 weeks."
- *Dr. Newburger, a dermatologist:* "You lumped together the devices for anonymity?"
- *FDA staffer:* "We did not lump them together. We are presenting the studies anonymously."

- *Dr. Newburger:* "I understand that, but my comment was one of your primary adverse event post-approval studies shows A, B, and C. You have a large difference in nodule/ mass formation. It's important for me to know what product it is. I don't think it's fair across the board to make any conclusions regarding Fitzpatrick types IV-VI when you don't know the interaction compared to the HAs, which have been studied more thoroughly. You can't really make those conclusions. So, perhaps what you want to be doing is setting up a standard protocol whereby these parameters would be followed in Fitzpatrick types IV-VI but adjust the duration of study depending on the mechanism of action and duration of action, on how it's metabolized in the individual."
- *FDA:* "We're presenting now what we have done and not necessarily what we're going to do in terms of what we plan to do in the future for these types of products as we get completed studies – get details for each manufacturer, but that would require us to give manufacturers notice that we're taking them to panel. This general topic meeting was intended to say, 'Here is what we're doing, and is it going in the right direction, yes or no?' I know it's disconcerting."

Malfunctions. Dr. Newburger asked, "You said that there were 93 reports of malfunctions. In my practice, we have seven dermatologists, all of whom are heavy users of injectable fillers, and we have reported more than 30 luer lock failures this year. I'd hate to think that there are only 60+ individuals in the rest of the country who have reported that. What evidence do you have that there is compliance (in reporting)?" The FDA's Product Evaluation branch chief said, "We do require by law that manufacturers report adverse events to us through the MDR reporting system. These regulations are upheld through a number of ways – one of which is inspections. The manufacturer has the liberty of determining whether a device adverse event is a malfunction, injury, etc., and they make the determination…whether or not they should report these to the FDA…(But) we sometimes can't enforce the reporting of these problems."

Event reporting delays. Another dermatologist asked about delays in event reporting, "When I was reviewing the website I noticed an extraordinary long delay before events were reported to the manufacturer and it actually made it to the FDA. Is this the kind of thing that would happen with an inspection?"

- *FDA product evaluation chief:* "In addition to whether or not a manufacturer does report, they are also required by law to report within a certain timeframe…and they can be fined."
- *Dr. Li, the materials expert:* "I have a question about the reporting of devices. Without specifying what particular device was reported on, can you tell us if the adverse events were distributed evenly through different products or is it possible that most of the adverse events came from one or two products?"
- *Another FDA staffer:* "The adverse events came from different products. There were some differences in the adverse events in the different brands but they were locked together for this presentation."
- *Dr. Li:* "I'm trying to calibrate the study to something. Is there any way to make that kind of comparison or association to see if you're in the ballpark or not? If you have no adverse event in the study, but many in the reporting system, that would tell us something about the study?"
- *FDA product evaluation chief:* "It is something we looked at; when the post-approval study is done the epidemiologist will often ask for a study on that particular device on a particular function."

Postmarket follow-up. Materials expert Dr. Li asked about follow-up, "The postmarket patients were followed at 12 and 24 weeks, is that correct?"

- *FDA staffer:* "The follow-up for the three post-approval was all 24 weeks and for the pre-market between 12 and 52 weeks."
- *Dr. Li:* "What do you know about he 24-week time period and the rate of degradation of a particular filler?"
- *Another FDA staffer:* "They are different compositions with different durability times…but unfortunately we're not talking about particular devices. We didn't look at degradation. We just looked at the primary adverse events and also some other things. Even if degradation did occur, which we cannot tell, they were not looked at, and they were not part of what these studies were designed to do."
- *Dr. Li:* "I see a lot of opportunity here." *(laughter)*
- *FDA product evaluation chief:* "For the vast majority of manufacturers, they are reported diligently and reported accurately."
- *Dr. Michael Olding, chief of plastic surgery at George Washington University:* "The panel is presented with some difficult questions. They are made more difficult by the fact that we don't seem to have a good handle on the numerator or the denominator. I think that we have to do something to improve the system for adverse event reporting. The FDA takes some responsibility for that as well as the physicians, and there has to be some easy manner to increase those numbers. Our decision-making is, for me, going to be difficult because we don't have a handle on it."
- *Dr. Newburger, a dermatologist:* "It's an attempt to accommodate the real world in terms of how these devices are used…That said, I'm excited that we can brainstorm

about how we can get a more accurate reflection of what happens in the real world."

- *Dr. Karen Burke, a dermatologist from Mt. Sinai Medical Center in New York:* "It's important to get some kind of protocol that everyone can follow. And when a study is done it should be done to track patients longer, because some fillers stay in the patient for more than two years."

Adverse event reporting. California plastic surgeon Dr. McGrath stressed the importance of carefully collecting post-market adverse event information, "From the discussion we've had about the MDR, it sounds like the incidence of very serious complications is very low, but since that's the case, and since all adverse events and incidences are low, the post-market studies are critical and need to be augmented. It's also extremely important to look at this by products, not as a unit, to separate them by their duration and other parameters, so we're looking at different things. And since reporting is going to be key…a standardized narrative would be very helpful. Perhaps if questions were asked about who is doing the injection and other things are asked when an adverse event is reported, maybe more information would be captured."

- *Dr. Erin Walker, a dermatologist from White Plains NY:* "I'm somewhat concerned at the amount of disconnect between what the FDA has presented and what is happening in the real world…The FDA needs to make the reporting of these adverse events much more simplified, easy to use among the using clinicians. I have not had the experience of making a report to the FDA, but I've been told that it's quite arduous and time-consuming, and there may be some other way to address that as well, to get more a accurate report from the general user and the public."
- *Epidemiologist:* "We have three highly respected organizations that are offering to work with the FDA and that's something to keep in mind."
- *Dr. Li, the medical device testing expert:* "The first issue of reporting is one that I actually haven't seen solved for any device in the U.S. The only example I can think of in the world is the Swedish registry for joint replacement… short of that I'm not aware of any system that could get the reporting percentage up…I don't see how that's going to be improved…We have no idea what the number of adverse events is in these devices – if there are really that many reports, that's 0.01% of all devices implanted, so I just don't see our way forward on that. And on the study, the study presented more questions than answers...We're blinded to the device so we're also blinded to the device variables. It's a single time, and there's no correlation of the results to any previous report, so I'm not sure what to do with the information in a postmarket study."
- *Ted Gooley PhD, a biostatistician from the University of Washington:* "The one thing I wonder about is how these studies are powered and whether or not there are enough patients studied to answer the questions that need to be answered, specifically safety…I'm struck by the small sample sizes."
- *Halpin, the industry representative:* "There is a pre-defined definition of when we report something as an MDR. Ninety-four percent of what is in the MDR system is reported by manufacturers; I'd think that we are doing a good job. But unless it is reported to us, we are not able to forward it and report it…With regard to post-approval studies, any guidance we can get to help us design these types of requirements into our pivotal studies so we can look at something like skin color…would be very helpful."

Trial variables. Dr. Gooley, the biostatistician, said that he was struck by the small numbers in the trials and asked what types of differences in populations are looked at in superiority or non-inferiority trials. An FDA statistician said that in non-inferiority trials, a full point is the minimal detectable difference, the FDA usually requires half a point and a full point is usually the minimum in superiority trials. She added that wrinkle fillers are generally powered for efficacy.

Dr. Li, the medical device testing expert, asked how variables in the devices are rolled into trial design, "For example, if one material degrades quickly is against one that doesn't degrade quickly but there is a size difference, how do you deal with that? Is it hidden in here, or is it an area that wasn't addressed?" An FDA staffer said that before a study begins the FDA usually has a sense of how long the product will last, "All of the products used are FDA-approved products and commercially available. The endpoints are also done as scale, so we have not observed a problem of some products offering a variation of five points vs. two. What we try to do is make sure that the patient receives an optimal cosmetic treatment." Dr. Li asked, "Do you use the number of units to get an effective treatment? Perhaps different patients would get different numbers of units to get to the same endpoint?" An FDA staffer responded, "Yes."

Trial endpoints. The industry representative said, "My takeaway is that these trials use both non-inferiority and superiority and are based on efficacy. In terms of endpoint analysis, most endpoints have been validated, and they're fairly sophisticated trials developed over time. For new indications one of the major questions will be for a first product in, what do they need to be compared to, if anything?"

- *Consumer rep:* "The main thing we have to deal with is safety. There are some areas of the face that will be rolled in easily – they are comparable to nasolabial folds, but other areas we have to work on."
- *Dr. Li:* "I understand that the trials done now are reasonably effective ways to evaluate the products, but it's not done in such a way that I could basically evaluate the materials because we're using different amounts over different endpoints, and although we walk away saying

this device is safe, it doesn't give me basic information about that material. So, each time that material is used in another indication or another amount, we have to do the same study over again. We're satisfying one question, but we never answer the basic question of evaluating a dose response for a particular material in a particular location."

- *Plastic surgeon and epidemiologist:* "I'm satisfied with the endpoints. They're reasonable. I also think that I'll be happy when ASPS (American Society of Plastic Surgeons) has their patient satisfaction scale. In the absence of that, we could use a patient satisfaction scale. With regard to new indications, I wonder if there are presentations given at professional organization meetings that we can draw on to see how these are being used off-label and perhaps get some guidance in that regard."
- *Dr. Walker, a dermatologist:* "I, too, have been satisfied with the endpoints, but the issue of off-label use is not being addressed and absolutely needs to be…Perhaps adding one additional site per product may be a way to move forward. The issue needs to be addressed because we are all using the products outside of the nasolabial folds routinely."
- *Dr. Karen Burke, a New York dermatologist:* "I'd like to see the data. I know the photographic data are good and patient satisfaction is good, but I'd like to see, instead of all the variability, a strike protocol that 'x' amount will be injected and evaluated at one month, two months, six months, and we'd do a measurement of dermal thickness on a prescribed place on the patient's face…I'd like to see some studies like that."
- *Dr. Newburger, a dermatologist:* "The algorithms used in the past have been terrific when we've used the products as wrinkle fillers, but generally there has been a change in the art, and these products are used more to provide volume in areas where it has been lost whether through disease, age, trauma, or congenital deformities. We need data. We need objective and quantifiable data. There are visual ways to validate scales whether in photographs looking at the measurements of how long a fill can be demonstrated or using some 3-D imaging systems, such as the Canfield Spectrum System. In terms of durability, since there are different stresses towards mobility in other areas, it may not be directly applicable. I, too, am looking for more data to look for persistence of response, durability, as well as safety."
- *Dr. Bigby, a dermatologist:* "Since these are by and large cosmetic procedures, I think that patient-centered outcomes are the most important and should be given the most emphasis. Patient satisfaction and quality of life are much more important than measured scales. Second, I'm not sure that getting FDA approval for an indication is going to change use much because the patients have already voted. They come in with lots of money in hand to have these procedures. They voted for having them, and I'm not so sure that getting approval is going to help the manufacturer that much. And third, I heard a statement that you can't study the biology by doing biopsies; however, you can learn a lot by doing studies on other areas and have it done on volunteers. So, that argument has no validity."

Sample size. Biostatistician Dr. Gooley said he is "still surprised" at the small sample size, "If the real true differences in efficacy are large, the studies will be powered, but I guess that raises the safety question with only 100 or 200 patients in an arm. I don't know how much confidence you have that one product is safe enough or safer than another product. That would be one concern I'd have with these small sample sizes."

- *Dr. Olding, a plastic surgeon:* "I'm not going to beat a dead horse particularly since I ride one most of the time, but the sample size seems amazingly small to me given the number of people in the U.S. who are getting the products injected, and I'd feel more comfortable having a large sample size. That is because there are so many variables. Even the term dermal fillers isn't accurate for where we put these. They're subcutaneous around the eyes, as deep as possible. So, there are so many variables that it's difficult to evaluate. But it's not an insurmountable problem. But it has to be addressed in terms of durability and complications."
- *Panel chair Dr. LoCicero:* "One thing we've heard about today is the different areas of the body and how those regions might be similar or dissimilar. The FDA does have guidelines on this. All the time they evaluate and pronounce things substantially equivalent. While we go on break, maybe the FDA could give us insight on how they determine how something is substantially equivalent. We're talking about different regions of the body."

PANEL CONSIDERATION OF FDA QUESTIONS

FDA introductory comments to the panel: Current labeling for dermal fillers states that most adverse events are immediately noticeable and temporary. Discuss the adequacy of the current labeling including whether patient labeling should be modified to include adverse events that may manifest several weeks to several months after the initial injection or those adverse events that may take some time to resolve, such as scarring and necrosis.

QUESTION 1. Should labeling be modified to include types of adverse events which were not observed during clinical study but are evident in postmarket adverse event reporting? YES.

Suggestions included labeling to include how many years experience there has been with each filler. The panel also liked the idea of a consensus conference including professional organizations. Dr. LoCicero, the panel chair, summarized, "We can all agree that clearly adverse events that occur after a

PMA need to appear in the labeling, and information concerning postmarket approval for that particular agent needs to appear in the labeling. We are somewhat divided. We won't vote, but we need to communicate that groups of devices may have similar reactions."

Panel comments included:

- *Dr. Newburger:* "Yes, it does help. It should be modified to include late developing adverse events and should follow the CDER model. Furthermore, the clinical studies are so small whereas drug studies generally have a much more robust population, and drug studies have a more well-defined endpoint…The size of the studies are such that we are missing events."
- *Epidemiologist:* "Since these products are primarily used on the patient's face, most patients are coming in to look better and if we know that a potential longer term adverse event such as scarring and necrosis can occur, I think patients should be informed of the possibility."
- *Dr. Burke, a dermatologist:* "I think there should be specified exactly how many years experience there has been with the drug…We postulate some of the long-term events might be very many years later, as in the case with silicone, so it's nice to know that something has been used for 7 or 15 years with no side effects, compared to something used for two years."
- *Dr. McGrath, a plastic surgeon:* "If you're saying that everything that we've learned from postmarket surveys should be on the label, I would say no because it depends on the product. If something is bubbling up with one product and not another, I don't think it should be on all the labels."
- *Boston dermatologist:* "These are highly popular procedures. How much impact will (label changing) have? But enforce labeling so that what is known about adverse events is included in the label."

A discussion ensued about how to stratify devices based on adverse effects:

- *Dr. Olding, a plastic surgeon:* "I think that it should be included, ultimately, but it depends on the quality of the post-approval study. We've been told that it's not comparative…We can go further regarding absorbables vs. non-absorbables – HA vs. non HA, silicone – and each has its own potential complications and adverse effects, and they should be stratified based on those effects."
- *Boston dermatologist:* "I agree – separating into classes."
- *Panel chair Dr. LoCicero:* "Who would we ask to define the class? Would it be the FDA's job?"
- *Dr. Olding, a plastic surgeon:* "I like the idea of a consensus conference. I would hope that something like that would be very important in helping decide these questions."
- *A New York dermatologist:* "I don't know if it's fair to even lump products made from the same molecule into the same class, because there might be something about the shape of the molecule – some shapes provoke immunologic reactions compared to another, but that is something that could be looked at."
- *Dr. Li, the medical device testing expert:* "Not to make this harder, but it's not simply the chemical makeup or composition of the filler, for example, the dose response of the particles to tissues, large amounts of a material compared to another. It doesn't always work out material A compared to material B. And HA has different cellular response whether I put it in bone or in cartilage. So it becomes very difficult to classify these devices. Every time you do that I can find a counter example."
- *Industry rep:* "Maybe working out a guidance document – industry, doctors, FDA – on how to classify devices and how you go about that."
- *Panel chair:* "Spreading the pain."

QUESTION 2. Considering that dermal fillers, in general, are administered to healthy patients as an elective aesthetic procedure, should FDA's tolerance for mild-to-severe adverse events be different than for devices that are intended for treatment of disease? If so, does the panel consider current FDA tolerance for serious adverse events be increased or decreased for products used for aesthetic use products?

YES, less tolerance for serious adverse events with aesthetic use products.

The panel agreed that the FDA's tolerance for adverse events should be lower for these devices than devices intended for treatment of disease.

Panel comments included:

- *Dr. LoCicero, the panel chair:* "These products have some pretty specific indications, and we know from other reports that injection closer to bone, for example, may result in a different type of reaction. That's really not the indication for the product. So, how can the FDA make a statement about an adverse event that occurs for an indication that is not what it's indicated for?"
- *Boston dermatologist:* "A product approved for an indication that becomes available in the open market often gets used for other indications and often they exceed the use of the indication (for example, thalidomide). I think that in that situation one can talk about the adverse effects when it's used for other indications and that has been done for example for neuropathy or birth defects. I don't see how this is a problem…It isn't clear to me what the FDA's tolerance of these things is. So you can go a long way in defining what is your tolerance because the actual rate of serious adverse events is relatively small. So, what

exactly is your tolerance for adverse events? What level is unacceptable, and what level of study would you need to find out what level of frequency exists?"

- *Dr. Li:* "If we had a full reporting system it's unlikely the adverse events would decrease, so what we're reporting is an iceberg's tip of adverse events. It seems as if it would be a disservice to the whole reporting system if we downplayed the importance of those adverse events. If we had a higher tolerance for the adverse events of these fillers, if you dismiss them or lower tolerance, may say nothing about harm to patients…I'm not sure how much the labeling controls use…The vast majority of use is off-label. It's an odd device where the largest use appears to be on-label. So, I don't know if there could be stronger labeling. These are off-label uses."
- *Karen Rue RN, the consumer representative:* "(Using fillers) is pretty much an elective thing for self esteem. What we tolerate for people with pathology and disease is different, and I feel that we don't have a grasp on what the adverse effects are…Therefore, I feel that we are not holding the companies to the same standard, and I think we should have less tolerance for severe adverse effects. We shouldn't allow as many. We have got to get the consumer this information, so that they don't have to dig and dig – so they know what the adverse effects are, and what we tolerate."
- *Epidemiologist:* "I see in my practice that if a patient goes in for an elective procedure, and there are complications, the psychological ramifications can be significant. I would agree with the consumer panelist that we should have less tolerance for serious side effects…We need a better reporting system…but tolerating adverse events is not in the best interests of the patients."
- *Dr. McGrath, a California plastic surgeon: "*I thought the question was should the FDA's tolerance be different…I think it always has been. There is a recognition that there is a difference between illness and quality of life applications. When we get to the next part of the question, should the current tolerance be increased or decreased, I'd say neither. I think we are at equipoise now."
- *Dr. Newburger, a dermatologist:* "The only recalls I know of are threads, and I'm not aware of anything other than severe infection with fillers. From the point of view of ethics, I think tolerance should be decreased because these devices are not designed to make a patient walk or preserve a heartbeat."

QUESTION 3. What would be the most effective method or combination of methods for FDA communication to physicians regarding the postmarket information collected by FDA, such as concerns related to off-label use, delayed onset of adverse events, and less frequent but severe or unexpected adverse events?

The chair summarized the panel thoughts on this and on Question 2: "The panel seems to agree that at a minimum there should be a **listing of the adverse events** that occur, and we are not in a consensus as to the level of tolerance that there should be, but we are in consensus that **wide dissemination of information** should be accomplished with a wide variety of methods (including industry organizations, the FDA, informational brochures, etc.)."

Panel member comments included:

- *Dr. LoCicero, the panel chair:* "This really begins at least to some extent with the consumer."
- *Dr. McGrath, a plastic surgeon:* "We're talking about adverse events, so obviously the package insert (labeling), all the websites, manufacturer training materials and modules, and professional organizations."
- *Boston dermatologist:* "Communicating information about postmarketing events, you should start by doing a better analysis of what those events are and at what frequency. I'd start by looking at it by product and then by location."
- *Dr. Newburger:* "I have a question about the most effective methods of communicating with physicians. One way might be to get one of the myriad of celebrities affected to be a spokesperson, and I can think of half a dozen right off the top of my head."

QUESTION 4. Based on clinical evidence and post-approval studies, is there sufficient evidence to conclude that evaluation of dermal fillers in patients with Fitzpatrick scale scores I-III can be generalized to patients with Fitzpatrick scale scores IV-VI? Unanimously NO.

QUESTION 5. Should clinical evaluation of dermal fillers consider patients with Fitzpatrick skin types I-III and IV-VI as two distinct populations with potential to exhibit different safety profiles?

NO, but more patients with Fitzpatrick skin types IV-VI should be studied.

The FDA said that a guidance document might be fine for premarket study, but what about post-approval studies, which are generally based on what questions need to be addressed by that product?

- *Dr. LoCicero, the panel chair,* who noted that recruitment has been a problem in darker-skinned individuals.

"What's coming up is let's get everybody in there, but we may have to do it for different times and stratify it, and so on. That leaves the industry with not knowing who to go to in order to develop these studies."

- *Industry representative:* "We should be looking forward rather than backwards, and some products may have been improved a long time ago. I'm not sure if we have to go back…but looking forward...a guidance document that focuses on clinical study design would be useful."
- *New York dermatologist:* "Moving forward just with adequate study design is important. Some of the older products were short-lived, and even in the timeframe of their effectiveness, adverse events resolved by the time they disappeared. The older products don't seem to be as much of an issue as the newer products that are about to come into the marketplace."
- *Consumer representative:* "If we got better adverse reporting in general, that would indicate whether or not we'd need that."
- *Boston dermatologist, an African American,* who said that the two populations should ***not*** be considered separately since there is a large overlap among the skin types. "The range is quite broad, and the bell curves interlap. Everyone has this idea that keloids and pigmentary problems are more common the darker you get, and that is a mistruth based on many years of clinical experience. The overlap is too great. The thing to accomplish is to know what the safety profile is among the people who get the product. Study design should include that spectrum of people in adequate numbers."
- *Another African American, a dermatologist from New York:* "That is the disadvantage of the information before us. There are not enough numbers, and we need to get more diversity…There is no difference, and these are ***not*** two distinct populations."
- *Dr. Gooley, the biostatistician:* "It seems as if the randomization could be stratified on the Fitzpatrick score to ensure that you didn't have a higher proportion of agents with higher Fitzpatrick scores in one arm compared to another arm."
- *Dr. Li, a medical device testing expert:* "If I'm unsure about the results from a pre-market study, I'm not sure I can dismiss a postmarket study…This has to be done on a product-by-product basis. So, I think it could be misleading to generally just use the skin types as a way to classify response…It's not just dose response but maybe a timing issue. To generalize the study at this point, where we don't know a lot of the basic information, could potentially lead us to wrong conclusions."

QUESTION 6. With respect to current study designs for pre-market approvals

A. Are current wrinkle severity and global aesthetic improvement scales adequate?

B. Are particular evaluation methods more predictive of device effectiveness in the general population than others?

C. What is the value of masked vs. non-masked evaluation and live vs. photographic evaluation?

Panel members generally agreed that **current wrinkle severity and global aesthetic improvement scales are adequate for wrinkle assessment but not for new indications**. One surgeon said that style also comes into play, making effectiveness even more subjective and patient-oriented. Suggestions included new methods to assess patient satisfaction, such as one that is being constructed by one of the professional organizations. Panel members thought masked evaluation, live evaluation, and photographic evaluation all are useful. Those who gave an opinion said that unmasked evaluation is more biased than other methods. Several panel members repeated their concern about the small patient populations in the studies.

Panel comments included:

- *California plastic surgeon Dr. McGrath:* "With regard to using the scales, those have been adequate for the wrinkle assessment, but I think now that we're talking augmentation and volume enhancement, we're going to have to add something to that. A global enhancement improvement scale would have to be looked at but it would have to be further defined…Blinding will be useful when it comes to volume enhancement. These will be much more subtle changes. This will be a learning experience. If people put a certain amount of a product into perhaps building up the chin, how much do you need to see a difference? It will be very useful for people to be blinded to the befores and afters."
- *New York dermatologist:* "What we want is patient satisfaction with safety. We can make quantitative measurements in today's age about how effective enhancement is at various time points. That is of interest. I advocate quantitative measurements…Everything should be masked – it removes one subjective barrier."
- *Dr. Gooley, biostatistician:* "I wonder why a little more attention isn't paid to safety as a primary endpoint here… The community that is expert in the area should decide the appropriate measure to use. The statistician makes sure there is a meaningful way to analyze it."
- *Dr. Newburger, dermatologist:* "The current scales are fine for nasolabial folds. But we have to go toward new evaluation methods. I believe that they should be quantitative. But I think we have to talk about the patient populations, which vary. You're going to be looking at people who have disease, trauma, or want a change

because of style or age corrections. What's acceptable in New York is natural compared to the left (West) coast or the South, and it depends on the ethnic group what the style is. So, it's not fair to use a global assessment scoring system. Understanding that style or definition is something in the eye of the beholder, there still should be an effective way to look at effect."

- *Plastic surgeon and epidemiologist:* "I agree with you in principle, but there are very few quantitative scales that are appropriate for this population. For example, satisfaction scales that ask about the face, thighs, etc. It is difficult to find a scale for facial corrections other than nasolabial folds…Perhaps a scale that addressed those areas of the body, such as cheeks, could be developed. It could be a three or five question scale…but I'm glad that plastic surgery folks are working on something because we really need it in this area."
- *Dr. Olding, plastic surgeon:* "Now that we're moving to volumizing of the face, the vast majority of my patients have concerns about the volume in the face. There is no fold to correct. There is no measure. But there are very good photographic methodologies available to measure pre- and post-op. One of our members is doing a study for us on aging over the years. That would be one way of determining the overall value. I don't care how it corrects something; I want to know will it fill up the face and more importantly how long it will last. I have to be able to tell my patients which one lasts the longest in this area, and if we can have an objective analysis of that volume, that would be helpful."
- *Halpin, the industry rep:* "When studies of nasolabial folds were constructed, the 5- or 6-point scale was developed. It started with target photographs, and those were developed into one scale…The best on the scale was not maximum correction but optimum correction. The photographs were good for educating how to use the scale, but the question is whether you take the scale and compare it to a photograph vs. a live face. I think it would be very much within the industry's capability to work with academia to create those types of scales for those areas. Ultimately the goal is whether the patient is satisfied. Did they get the correction they wanted? And when you look at the face, is that what you wanted to achieve?"
- *Panel chair:* "We're going to be going with digital photos. How will you deal with this in terms of evaluation?...Is it still necessary to mask our evaluators? Physicians are good at seeing subtle differences."
- *Dr. Li, device testing expert:* "In other areas where there are subjective rating systems, we've found that multiple observers often give more information than blinded (observers)…If you can't do a blinded or masked protocol, multiple (observers) might be an alternative."
- *Dr. Gooley, biostatistician:* "If you have multiple observers, you have to alter the statistical analysis a bit, but it is doable."

QUESTION 7. Are current safety evaluation methods adequate? Should current safety evaluations be expanded to include larger studies to detect less frequent adverse events? Studies of longer duration to detect delayed onset of adverse events? Histological evaluation of biopsy samples?

The panel was in favor of larger studies.

Members said that longer studies will be needed for fillers that last longer but admitted that those studies may not be feasible because of the problem with subjects lost to follow-up. The panel said that there are advantages to histology, although some members said that getting samples would be problematic. The panel chair said, "In the safety area, we need to work out some of the obligations of the consumers to report adverse effects."

Other panel comments included:

- *Harvard dermatologist Dr. Bigby:* "Clearly if you're talking about events that occur less than 5% of the time, none of the studies has been adequate, but we don't really know what the threshold is for considering something too frequent or too serious."
- *New York dermatologist:* "My immediate answer is yes, but I'm concerned about products under consideration. There should be some way for the study design to reflect the duration that is intended and have some parameter to reflect what a longer duration might mean. If a product is supposed to last for six months, how long should it be studied – one year or two? I'm thinking that duration might be double or triple the time. There's no way to quantitate that. If the duration is 12-18 months, what's an adequate duration to detect these adverse events' delayed onset, which is a major concern?"
- *Dr. Li, materials expert:* "Most of these materials have a long history in medical implants. I'm always interested in looking at histology, but why look at it if we can't associate it with some significant clinical event?...It seems to be more of a research project on the histology and less of a clinical endpoint that we're trying to reach. Clinicians would have to tell me that there's some endpoint that relates to histology. For the other things, unless there is some significant clinical event that we're trying to explain, just looking won't advance our knowledge…I'm not quite sure some patients don't do that great…If the companies want to get to the bottom of this, get some basic research (needs to be) done…I don't feel we know exactly what happens to these materials over time…We don't know how much is left or where it went. Some is found all over the body – in the lungs, lymph nodes, and

we have no idea where these particles are going. Maybe they're not doing any harm but we don't know."

- *Industry rep:* "Safety studies are specific to the material, and most manufacturers have a lot of preclinical material on their products…We actually do a lot of preclinical testing, and some of that information would be available in order to determine what is happening to that product."
- *Consumer rep:* "I don't know that the trials would vary as opposed to getting consumers to give feedback. We can study things forever…but it's up to consumer education."
- *Plastic surgeon and epidemiologist:* "I think a very long study would create more problems, and patients would be lost to follow-up. I think that asking a patient to submit to a facial biopsy is going to be problematic to say the least …I think that histological evaluations are not going to be done."
- *Another dermatologist:* "Histology is of tremendous import. There is nothing wrong with placing the implant in a forearm or insignificant area and seeing what happens over the course of time. If something causes collagen to grow, is that collagen or is it scar tissue? If I try to inject, there is resistance as if I am trying to inject through scar tissue. This is helpful going down the road. Also, if you don't know how a device is metabolized, you are at a disadvantage. You need a lot more basic information, and if you have it, the longer term studies might not be as necessary."
- *Dr. McGrath, plastic surgeon:* "We do want larger studies …not embarrassingly small studies of 100 patients, but to get at the rare events that will have to come somewhere else. For non-asborbables, some of us are saying that we want to see them longer, but we're not necessarily talking about the ones that have gone through approval."

QUESTION 8. Do current inclusion/exclusion criteria allow for collection of safety and effectiveness data that is consistent with and predictive of your experience with dermal fillers in the postmarket setting? Does the current exclusion from clinical study participation of subjects who have had recent cosmetic procedures impact manufacturers' ability to collect complete safety information?

The panel agreed that the exclusion of patients who have had recent cosmetic procedures **hurts the manufacturers' ability to get complete safety information**. As patients get more and more different procedures, such as Allergan's Botox (botulinum toxin A) and a filler, different adverse effects may occur.

Panel comments included:

- *New York dermatologist:* "You can't study one filler on top of another. Although that will happen in the general population, you can't do that in the study when it comes to the longer-term fillers available today."
- *Medical device testing expert:* "It may affect the overall global aesthetic evaluation, too."
- *Panel chair:* "We may have to limit it to less than 40 procedures." *(laughter)*
- *Plastic surgeon and epidemiologist:* "If you have Botox and something else, your satisfaction may be higher. But if we don't allow them to use multiple agents, are we going to know if there's any interaction?"
- *Dr. Newburger, dermatologist:* "One of the individuals who wrote a letter to the panel suggested that patients be given a registration such as one we have with Accutane (Roche, isotretinoin), and that way if adverse events were reported, you could see which were with multiple fillers. In my practice, the few who have had persistent swelling, each has said that they may have had silicone injections 20 years ago or previously injected devices. That is a common denominator in the ones I see. In terms of exclusion and inclusion, when I get the consent from the rheumatologist, we inject in patients on anticoagulant therapy, and we have had no issues whatsoever."

An FDA official asked, "We talked about other fillers, but I thought I found repeated application of the same product for the same area, and how does that impact your discussion at this point?"

- *Dr. Newburger, dermatologist:* "One of the issues we encountered is when people have had a filler in the lip area, a very thin dermis, and have had multiple injections, that it is very difficult. You'll tend to have more lumps develop because of the scarring that develops in that area after multiple procedures. Scarring can change the picture over time."
- *Dr. McGrath, plastic surgeon:* "You're going to have to sort out the patients who have had repeat treatment and those who haven't. If you follow for five years, you'll have to sort them into two groups – one for patients who've had it once and one for those who have had it multiple times. That's unavoidable."

QUESTION 9. Are current methods for determining sensitization potential inadequate (i.e., clinical study methods such as Magnusun-Kligman Maximization test methods) and are clinical study methods of evaluating adverse events in subjects after two dermal filler injections adequate? Should study methods be designed to be more reflective of the frequency of dermal filler injection in actual clinical use?

No consensus.

The panel chair summarized, "We don't have a consensus or agreement on any suggestions. I'm concerned that we're going to make a recommendation that isn't going to happen. After this, we're going to have to make sure that those societies that proposed this will go along with the consensus groups."

Panel comments included:

- *Dr. Newburger:* "Current methods are adequate. To have a true allergic reaction is certainly very, very rare. We have not seen one and in our community I have not heard of any true allergic reaction."
- *Dr. Li:* "We seem to be going around in a circle. If we don't know the histology, and we do an animal test, we're going to get animal response, but unless we know the data in a person, I don't know the connection."
- *Dr. Olding:* "For many of the HA patients, instead of going from empty to full, they go partially empty to full, and I've had patients since Restylane was approved that have been getting that the entire time."
- *Dr. LoCicero, chair:* "So we'd say it's already happening in the real world?"
- *Dr. Olding:* "Certainly."
- *FDA official:* "Those questions have been going away with time."

QUESTION 10. If a post-approval study is recommended for current indications for use, please recommend approaches or strategies that would properly evaluate safety in this population (two or more dermal filler injections), including study design, comparison group, duration, assessment method, and safety endpoints.

No consensus.

The panel chair summarized, "If I were the chair of a hospital committee, I would table this and form a subcommittee. (*laughter*) I'm afraid that's where we stand. On this question we really need a consensus panel. But who should sit at the consensus conference table? Industry, consumers, universities, academic societies, and the FDA."

Panel comments included:

- *Dr. Li:* "I'm not exactly sure how to do this. It seems as if it's not clinically sensible to set an amount injected and make that across the board for every patient. That takes the effectiveness feature out of it. But you have other variables if you go to effectiveness. With that aside, it seems as if the effectiveness variables are well discussed and well handled, but on the safety side there seem to be some other factors that could be included for evaluation."
- *FDA official:* "For each product, there are short-term and long-term questions when you're saying a product is safe and effective to go to market. Are there long-term issues? I've heard that training is an issue."
- *FDA epidemiologist Shoaibi:* "The objective of all the post-approval studies – 3 studies for 8 products – was safety. Aesthetic results were not collected for two of those studies. The objective was safety."
- *Dr. Olding:* "Two scenarios are if you inject a patient once, you can follow that patient long-term. If more than once, there are changes that are in and of themselves different than what would happen with one injection. But it reflects clinical practice."
- *New York dermatologist:* "I think a long-term study would be indicated for a device that is not absorbable. Things that won't be reabsorbed should be looked at longer term. And the point is that we don't see small effects that aren't frequent that are serious and might come later. It may be worth following people who have had something injected that is non-absorbable followed for some time. So, you want longer times for non-absorbable implants."
- *Panel chair Dr. LoCicero:* "The FDA and companies have been beaten up a lot on these postmarket studies, and now we have no recommendations. Please, someone."
- *Halpin, the industry representative:* "It seems as if we're being asked for a one-size-fits-all design, and I don't think we can do that in one meeting. It may be better on a case-by-case basis as you're seeing new products. That may be part of what we're struggling with."
- *Dr. Gooley, biostatistician:* "Every attempt ought to be made to address these issues in the pre-market studies. The pre-market study should be designed to try to minimize the questions that might come up in postmarket studies."

QUESTION 11. Can the use of fillers for augmenting tissue volume and recontouring tissues, such as non-surgical rhinoplasty, lip augmentation, chin and nose contouring, cheek augmentation, under eye injection, and hand volume restoration, be considered an extension of filler use for wrinkle correction? What areas of the face are dissimilar to nasolabial folds in terms of tissue structure and physiology?

The consensus was that there really is **no way to translate the data to another area**, at least not in a short time period.

Panel comments included:

- *Dr. Li, medical device testing expert:* "Some of these devices in the peri-orbital area don't work that well. I felt that we know so little about the mechanism of action in these devices that it would be a mistake to use in an area other than a nasolabial fold to be similar. In every case, I would want some study to be done…Part of the difficulty here is that we don't have basic information. If we know the tissue response in the cheek compared to the nasolabial folds, then you wouldn't have to test it. But I don't know how otherwise to be safe other than to do new safety tests every time."

- *Dr. Newburger, dermatologist:* "I agree. It's not analogous to placing filler in the dermis to cartilage, etc. There have to be separate studies. If it is one or two folds, I might consider it similar, but the majority of these are not the same. Certainly, hand volume restoration is a completely different circumstance…I think that nasolabial folds are going to act similarly to the area around the mouth. I don't think they are analogous to tear duct, peri-oribital area, or mellar or submellar areas."
- *Harvard dermatologist Dr. Bigby:* "The answer to the question is no. However, there is a large body of use of these products in those other areas, and not much of a signal has been detected in terms of adverse events occurring…from the physician's perspective."
- *FDA official:* "Some of these are dissimilar. Are there things that are similar? Cheek augmentation? Chin augmentation? Are there things that can potentially be grouped together depending on location or type of material?"
- *Dr. McGrath, plastic surgeon:* "If you look at the product, a lot of the questions are going to be the same no matter where it's used. You have to sort out what ***not*** to look at. But things that are translatable are effective on other anatomic structures, the technique, and so that's what you're going to be focusing on. I wouldn't separate it by geography. I'd say what do you need to look at and what don't you need to look at."
- *Industry representative:* "Industry would be open to that, but part of industry would like to understand what are the hurdles to get another indication. Instead of recreating the wheel or starting from scratch, but using the information they already do know about the product?"

QUESTION 12. In the design of clinical studies for new indications, what safety and effectiveness endpoints would you recommend? What are some clinical issues that would need to be addressed (i.e., device migration, local tissue response, chronic inflammatory response)? What would be the best control? Should the FDA consider controls that are accepted as current standard of care? Specifically, for lip augmentation what treatment could be considered standard of care and thus considered as a possible control? When there is potential for larger volume and/or repeated injection of dermal fillers in less than six months, would acute and long-term systemic toxicity studies be warranted?

The panel agreed that this question would take another day to answer.

Panel comments included:

- *Dr. McGrath:* "This is a very complex question. Each area will be different. Say for hands, you'll have different safety and efficacy endpoints. This would be a very difficult question to answer globally."
- *FDA official:* "What about lip augmentation, cheek augmentation separately?"
- *Panel chair:* "Do we have another day?"
- *New York dermatologist:* "Not only are these different anatomic sites, but these special things – lips, cheeks – are incredibly technique-dependent, and no one will go in and do it without very careful thought. These will become common, but not the most common, ways of using implants in large populations…There are areas that are incredibly sensitive, such as the under eye area and the base of the nose. They should be evaluated very differently. Technique and type of filler are extremely important, and it's very variable, the molecular weights, and viscosities of the same filler."
- *Dr. Olding, plastic surgeon:* "All of them except perhaps hand restoration, it's more than correcting a fold or wrinkle, it's a global aesthetic appearance, and so patient satisfaction scales are going to be very important."
- *FDA official:* "A lot of the wrinkle fillers have not looked to see is there is any impact on nerve sensitization…If you have loss of sensation in the hand, you have loss of function…Should these be incorporated into the studies?...Are there things unique to these indications in addition to global assessment, as in, is there a functional side to their use?"
- *Dr. McGrath:* "For us to say we can come up with some things to suggest today is presumptuous. We have to look at each anatomic site. But, yes, certainly different anatomic sites should be looked at."
- *FDA official:* "I'm going to push one more time. Should there be functional evaluations along with cosmetic assessment for hand and lips? We get those questions all the time."
- *Dr. Newburger, dermatologist:* "Function is incredibly important in those areas. Because of the unique anatomy in the peri-orbital area, it may become a problem with repeated injections and scarring that occurs. With lips, over time the scarring will become much more evident five or six years later. Also there is an issue where I've seen a number of people reporting sensory deficits with peri-orbital injections. People tend not to report their adverse events in publications, or they are just dismissed as anecdotes. Many reports are the equivalent of white papers sponsored by industry. But the key is to ask the right questions before you start."
- *Plastic surgeon and epidemiologist:* "Satisfaction is going to be directly related to function."
- *Dr. McGrath:* "Why is the FDA asking about clinical studies? Is there going to be an interest in doing clinical studies to look at what are currently off-label uses to make them on-label uses? Why are we venturing there at this point?"

- *FDA official:* "There has been interest expressed by companies in potentially examining (other) indications, and we're looking at that. The purpose of a general topics session is to learn how to apply what we've seen to new materials."

QUESTION 13. If a post-approval study of new indications is recommended, what strategies would properly evaluate safety? Suggest the appropriate study design, comparison group, length of follow-up, validated assessment method, and safety and/or effectiveness endpoints.

Panel chair: "We've addressed this, partially in new indications. One thing we haven't discussed is controls. Now, we're talking about a product that is on the market, and the sponsor wants an additional indication and what would be the appropriate control in a new area?" The panel struggled with the problem of what to use for control, **generally agreeing that choice for a control should be case dependent, but that saline is not usually a good control**.

Panel comments included:

- *Panel chair:* "You see a photo of a patient who has a product in one spot vs. saline. How long will it take you to figure out which is which?" A dermatologist responded, "Two seconds."
- *Halpin, the industry representative:* "Perhaps use the baseline of the patient as control. So, evaluate on the basis of change from baseline."
- *Dr. Li, medical device testing expert:* "Comparing to the baseline of the patients, it seems as if the injection site is always going to be different."
- *Dr. Gooley, biostatistician:* "Choice for a control could be case dependent. Sometimes using baseline would be appropriate and perhaps it wouldn't in other cases."
- *Dr. Newburger, dermatologist:* "You need a separate safety evaluation. There have to be safety issues. It can't be confined just to efficacy."
- *Dr. Bigby, dermatologist:* "If sponsors are asking for approval for new locations, one has to look at the experience with the product so far. The most important outcome is patient satisfaction and quality of life issues, and I feel very strongly that the safety issue in terms of design of the study is the most important. It must be powered sufficiently to exclude unacceptable adverse events, and the duration must have something to do with the length the product is known to stay in and the collected data you already have about the product."

DAY 2: ENERGY DELIVERY DEVICES

The General and Plastic Surgery Devices Committee discussed energy delivery devices for dermatology and aesthetic indications, but they didn't vote on any specific products. The FDA asked the panel to recommend how to evaluate the effectiveness of the devices compared to current legally marketed devices of the same type. The panel agreed that a measure of efficacy should be met, but they could not agree on what that might be for any indication. The panel had a difficult time making generalized recommendations, instead agreeing that efficacy measurements will differ with each device, but all efficacy claims must be substantiated.

There were two unspoken but underlying themes during the discussion: (1) a worry on the part of some panelists that some of the devices simply do not work, and (2) safety. While the panel was concerned about safety, it was unable to come up with any specific recommendations for the FDA in that regard.

Richard Felton of the FDA's Division of General, Restorative, and Neurological Devices, General Surgery Devices branch in the Office of Device Evaluation, opened the session with an overview of the types of energy delivered by dermatology devices and current indications for their use, regulatory issues, and new indications for use.

Felton said that the FDA has approved hundreds of energy-delivering devices for dermatological use, with devices delivering a wide variety of energy types and levels and covering a broad spectrum of device types from low level light therapy to mechanical massagers or CO_2 lasers. The types of energy delivered include:

- Light based systems, including lasers, LED, and intense pulsed lights (IPLs).
- Ultrasound, including focused ultrasound.
- Radiofrequency (RF).
- TENS.
- Microwave.
- Cryotherapy.
- Mechanical massagers.
- Combinations of the above.

Indications – all of which, except cellulite treatment, received marketing approval based on clinical trial data – include:

- Treatment of wrinkles, pigmented lesions, vascular lesions, acne vulgaris.
- Treatment of hair removal, hair growth, tattoo removal, temporary reduction in the appearance of cellulite.

Except for mechanical massagers, which are Class I exempt from 510(k) and have the "temporary reduction in the appearance of cellulite" indications, all the other devices with the indications are Class II medical devices, and most of them are prescription devices. When they were approved, most of

the devices were used in doctors' offices, clinics, or hospitals. Felton said that the main issue before the panel is the way to evaluate energy deposition devices "that deposit relatively low amounts of energy and produce a relatively small tissue effect." An increasing number of the dermatologic energy deposition devices are sold for indications that may not be medical in nature, such as "improves the appearance of the face" or "makes you look healthier," and the devices have moved out of doctors' offices and clinics and into spas and beauty salons, and cosmetologists and aestheticians are operating the devices as well as doctors.

New indications, either approved, in the literature, or on the internet include:

- Body contouring.
- Change in thigh size.
- Abdominal tightening.
- Skin tightening (neck, arms).
- Fat melting.
- Eyebrow lift/eyelid tightening.
- Lipolysis (not liposuction).

Validated or accepted measures of success do not exist for most of the new indications. For many, such as body contouring, skin tightening, and eyelid tightening, the amount of change is relatively small and is hard to measure. Indications such as thigh size and eyebrow lift may be measurable, but the change is relatively small, and Felton said that it may not be clear what represents "clinically meaningful change."

PUBLIC WITNESSES

Patrick Martin, **director of clinical affairs for Liposonix, a subsidiary of Medicis** which makes an ultrasound device for body sculpting, said that the company plans to submit its IDE (investigational device exemption) soon. The device already has a C.E. Mark. Martin said that clinical trials for such devices should ensure safety, result in patient satisfaction, and have a well-understood mechanism of action. Panel members were impressed that the clinical trials used histological data to prove that the mechanism of action was understood.

Martin said that patient satisfaction is an appropriate endpoint in trials, "A positive patient satisfaction rating should be accompanied by a safety profile and understanding of the mechanism of action. As for how clinical measures of improvement should be measured, he said, "It is not appropriate to require a demonstration of improved outcome because…the vast majority of procedures are done by patients in generally good health. There is no clinical reason to see an improvement in health outcome with a successful aesthetic procedure…but it is reasonable to expect that the studies show an understanding of the mechanism of action." In terms of safety, he said that tissue evaluation in pivotal studies or pre-marketing studies can demonstrate an appropriate safety profile. Secondary endpoints can include changes in waist circumference measurement.

Dr. Robert Weiss, dermatologic surgeon and professor at Johns Hopkins and president of the American Society for Dermatologic Surgery, **spoke on behalf of UltraShape**, an ultrasound device for body contouring. He is also an investigator in the ongoing IDE clinical studies of that device. Potential adverse effects depend on what type of energy source is used and the way it is applied, Dr. Weiss said, adding, "The UltraShape device mechanically disrupts and destroys fat cells…The study evaluates chemical profiles and examines blood lipid and liver function."

Reduction in fat thickness is the desired outcome with UltraShape, and a quantitative measure is necessary to assess the effectiveness, he said, explaining:

- **Subcutaneous fat measurement** can be assessed using CT images, and that is the gold standard because it distinguishes between tissue types. However, he said CT is not high on the list for clinical trial purposes because institutional review boards (IRBs) have problems with it due to the unnecessary exposure to ionizing radiation.
- **Ultrasound**, on the other hand, has always been used to measure subcutaneous fat thickness. It is portable and doesn't admit radiation. Dr. Weiss said, "We have two units. It's less expensive than CT, but it is very sensitive to the technician. If you press the probe a little too hard, you will affect the fat thickness. I've seen five people do it and get five different baseline measurements. We found that ultrasound, unless performed by the same person at a particular site, can be not that reliable."
- **Magnetic resonance imaging** (MRI) may be a preferred technique because it can also distinguish clearly, and it will work in rat models and in human cadavers.
- **Calipers** are low cost and useful if the same person uses them.
- **Photographic assessment** at baseline and regular follow-up in trials "is somewhat useful as long as we have the camera mounted, footprints on the floor, distance between subject and camera is identical all the time, and the lighting is the same. It can be done."

Dr. Weiss said that it is also necessary to quantify co-variants such as diet, exercise, BMI, and age, and it is recommended that some co-variants such as diet and exercise be controlled as much as possible. Adjusting co-variants may predict the effectiveness and may increase statistical power – the concerns of male vs. female, large person vs. small person. If you have a male with a 45" circumference and a female with a 35" circumference, and you cover the same area, you will get more profound change of measurements in the small female than you will theoretically in the large male."

He said that global assessments and patient satisfaction are secondary endpoints. Using circumference, weight, and appearance of the abdomen at Day 1 and at follow-up, "investigators can assess whether there is clinically significant or not clinically significant improvement, and we know that there are many ways to measure patient satisfaction, not presently for use in body contouring trials but in trials of other aesthetic devices. They are questions that could be easily asked in the clinical trial."

As for what kind of control to use in clinical trials, Dr. Weiss said, "The issue of sham control has been a difficult factor to incorporate because, in doing the actual physical treatment, you have to discuss it with the subject. The subject is sometimes suspicious that they don't feel anything during the sham treatment, so I'm not sure that's the best control. In summary, there are no definitive data available that can affect the ability to design clinical trials, and the manufacturer must be able to claim fat reducing effect."

Asked about the possibilities of scarring, Dr. Weiss said, "I have seen one picture from a patient treated in Spain where they were treated early in the development of the device, and there was excessive heat. There was a skin breakdown of about the size of a quarter, and that healed with excessive spiculate."

Panel Questions for Public Speakers and the FDA

The panel was impressed with the companies' efforts to collect data. During the question period, it became apparent that the UltraShape device requires three treatments compared to one treatment with the Liposonix device. Panel members were concerned about safety as well as the use of the devices in other areas of the body besides the abdominal area, resulting in possible misuse of the devices.

➢ **Data collection.** Dr. Newburger, a dermatologist, asked, "Are there any biopsies taken at an interval after treatment to show what the tissue looks like? The supposed liquefaction of adipose tissue, is that replaced by fibrose tissue?"

- *Dr. Weiss:* "We were not planning to do that at our site because this is a patient population that is trying to achieve aesthetics. I believe that the company has short-term data from abdominoplasty – just prior to where we had some immediate results – but I'm not sure how much long-term biopsy data there are."
- *Liposonix's Martin:* "In our studies of abdominoplasty patients, we harvested any time from hours after treatment to 14 weeks after treatment. We saw immediate effects and saw resolution…of those lesions over time. We have data to 14 weeks past treatment which demonstrated… remodeling of the tissue. Is it replaced by simple adipose tissue? This area cannot be felt; there is no unevenness of the skin."
- *Dr. Newburger:* "Both of you are presenting much more detailed protocols to study the mechanism of action and safety and efficacy profiles of these devices than I've seen before with similar devices. And (with) the 510(k) pathway, my understanding is that, because of its invocation of least burdensome route, companies can really use the equivalence route and not provide essentially any clinical information. Also, am I correct that you're asking to have the path to market become generally more rigorous? Is that correct?"
- *Dr. Weiss:* "This is certainly the most rigorous study for a device that I've ever done. I think that the bar has been very high…I think we'll actually have real data on a new device."

➢ **Treatment frequency.** A New York dermatologist asked, "How frequent are the treatments and are there long-term follow-ups? How sensitive are these instruments? If a person did one area more than another, would the clinical result be uneven? This is important for devices with no medical person overseeing their use."

- *Liposonix's Martin:* "Our device is intended to achieve the intended result in a single treatment. We have followed patients out for six months in pilot studies. I don't have data beyond that at this time. Regarding the user effect on the patient, I believe that both of the products are designed to limit the treatment options for the uses, so there is not a great deal of change in the energy output. The user of our device can only adjust the device to energy levels that have been shown to be safe in pre-clinical and pilot studies. We have done retreatment of patients and animal models to simulate inadvertent retreatment of an area, and it has had no effect on histological data."
- *Dr. Weiss:* "In terms of treatment application, with the UltraShape what they've done is created a computer program using a video camera and positioning dots on the border of the area of treatment. It's almost like a video game. There are dots on the screen, and you slide the device – the weight is the pressure and minimizes individual variation – and the dot turns green when it's ready to fire. You make sure that you uniformly apply the energy. In terms of the number of treatments, it is three in our clinical trials, given up to a month apart, and the follow-up is going to be three months after the last treatment."

➢ **Length of studies.** Asked how long the studies should last, Martin said, "For our proposed clinical study, because we have seen stable results out to three months with no change, our proposal is to have a three-month trial monitoring patients to three months. The endpoints we have suggested would include for efficacy the use of a patient satisfaction survey as well as waist circumference measurements. Patient satisfaction we still believe is an integral part of the assessment

because even if they achieve a 3-4-5 cm reduction, if it doesn't look good to the patient, it won't be a successful procedure."

- *Dr. Weiss:* "We're using MRI as our most objective measure of calculating volume at a specific anatomic landmark slice three months after the last treatment… Liposuction has maximal effects at six to 12 months. With these devices it's more like three to six months, and then I find out as we go out longer that people say, 'This gives me license to eat whatever I want.' People come back a year later after liposuction, and they've gained five pounds. So, there's a sweet spot where you get maximum results from the procedure, and then you don't get into too much of what the patient is doing on their own. It's a difficult issue, and I think we've chosen the correct end-point."
- *Martin:* "We establish three months as an endpoint. We've also seen during that time a solid safety profile, looking at claims for clearance that would be indicated by our clinical trial and looking at long-term durability of nine to 12 months or more."

➢ **Efficacy.** Dr. Li, a medical device testing expert, asked, "Are there any limits to the length, width, and depth of the amount of tissue that you can ablate? What are the limitations?" Dr. Weiss responded: "With the energy setting limitations on the device I believe that each spot is a few mm area, and I'd have to get clarification 3-4 cm below the skin surface. But by changing the design of the transfuser in terms of the membrane that focuses the ultrasound, you could probably adjust to different depths in the future. Now, it is limited to one depth and defined tissue effect at a certain energy level which are being employed and which are being tested in abdominoplasty."

➢ **Pain.** Liposonix's Martin said, "It is tied to patient anxiety. Some patients sleep through it. Patients who come back for a second time report less pain because they aren't as nervous. Patients in clinical trials have reported that this is much less pain than hair removal." Dr. Weiss said, "Many patients feel almost nothing and say, 'Oh I feel it a little bit, just a little less than with laser hair removal.'"

➢ **Patient satisfaction.** Asked how patient satisfaction is measured, Martin said, "We have developed some patient satisfaction questionnaires and recognize that these are non-validated instruments, but we have looked at some validated instruments for patient assessment, and we and our medical adviser didn't feel they were necessarily appropriate – not optimized for body contouring."

➢ **Treatment areas.** Asked if the devices would be used in other areas besides the waist/stomach area, Dr. Weiss said, "The company has heard of lateral saddlebags done…and with careful mapping and all the limitations that we're discussing, it can be safely applied to other areas of fat by an experienced user, but I'll leave it to the company to address that." He added that he is not aware of any different mechanisms of action for the devices other than what has been seen.

- Martin said, "We have only done histology on abdomino-plasty flaps. However, talking to our pathologists and medical advisers, there is no reason to believe that the mechanism of action would be different in other areas of subcutaneous fat, assuming that we are treating only the subcutaneous adipose tissue. In our preclinical studies, we have done work to examine if any ill effect from the treatment if inadvertent treatments occur into bone or muscle and because entry levels are sufficient to cause a limited amount of damage. You can see damage in the tissue, but again there are safety mechanisms in the machine to give feedback on the reflectivity that would trigger a cutoff outside the safety areas. That being said, we rely a great deal on training and education to make sure the users avoid that situation. This is the effect in subcutaneous adipose tissue, and that is what we should be treating."
- *Dr. Newburger:* "I believe that these will be used to treat double chins and because of the intricate anatomy in that area that there will be issues one will have to deal with. So, hopefully labeling and teaching will cover that to avoid those inevitable consequences."
- *Dr. Weiss:* "Yes, I agree. Wherever there is a way to misuse a device, someone will try to figure it out, and it's up to the engineers to make sure that can't happen. With contact sensors, it's a pretty big delivery thing, and it would be hard right now in the present form to try to treat chins. Obviously, people will try, and we will make sure they don't do it, at least on U.S. soil."
- *Martin:* "Our treatment head is too large to be used on anything other than what we call the 'wide open spaces' of the body. It would require a big change to make it accessible to smaller areas."

➢ **Efficacy measurements.** FDA officials said that they were not interested in specific devices, but on proposed indications for use. One said, "Our attempt is not to discuss specific devices here. Our interest is to get feedback from the panel on indications for use. We have a laundry list of all possible energy-producing devices that we will be asked to review for expanding dermatologic use…We are seeing this new laundry list of claims which are being added or requested (for indications such as) body contouring, change in thigh size, abdominal tightening, fat melting, and lipolysis (not liposuction but use of a device to melt fat and leave fat behind). Some of these indications have already been granted. Some are still being asked for. We have granted a change of thigh size for one company – one thigh control, one thigh treatment. (To measure the change, we used) measuring tape, with the same person measuring, and demonstrated that the side treated had significantly greater decrease in thigh size than the control side."

The official continued, "On the other hand, we've had people look at eyelid tightening, and with the probes, it can't be measured. Eyebrow lift is another area like this. In these cases, we've discussed with companies ways to develop their own ways – basically using photographs showing 0-100% improvement, trained physicians on those photographs, check reproducibility to physicians, use those photos as a template to look at before and after treatment…Fat melting is another one that we're struggling with. We've asked the companies to do blood chemistries to show that when you 'melt fat,' either releasing fat from a fat cell or melting it, that won't cause problems down the road. So, yes, our requirements seem to be getting a little tighter. The question is how do you objectively measure these effects? All you have to do is raise eyebrows a little bit, and you have an eyebrow lift. Smile and wrinkles go away."

He continued, "When you look at the outcome, the follow-up, who should do the evaluations? Should it be physician driven? Should the investigator be making the evaluation himself? Should it be blinded physicians coming looking after treatment? Is it the patient who is the important person or should we get the companies to develop measurement tools?"

Asked how many new devices are "me-too," an FDA staffer said, "Most of what we are seeing today are ***not*** 'me-toos.' That is what we're struggling with. What we're seeing most are new devices, new technologies…They have all been asked to do clinical data. All the fractional lasers are being treated as new technology. They are not 'me-too.' The initial ones have all provided histology, and as they've added claims for wrinkles or miasma, they provide data."

➢ **Endpoints.** The FDA staffer, as well as several panel members, said that photography is not a satisfactory efficacy endpoint. The FDA staffer said, "You can alter any photo by altering the lighting. Remove or add whatever you want to have there." A California plastic surgeon said, "Speaking about the new indications, I think that a lot of these are very confusing to clinicians. We're being asked by patients about them whether or not we decide to use them, so it's very important to have a clear-cut picture in mind about the effectiveness of these new things. We need to have endpoints where there is some proof of effectiveness and some sense of how to quantify that for our patients and what they should expect. We have to ask for very clear information about safety parameters, and I'm particularly interested in tissue effects and systemic effects."

➢ **Safety.** Dr. Li, the medical device testing expert, said, "The idea of calling these 'low energy devices' is a little misleading. If you're a cell, it's not particularly low energy. You're killing cells with these devices. They are high enough energy to do harm if you misuse them intentionally or unintentionally, so to think that something is safe because it is low energy is a mistake."

PANEL CONSIDERATION OF FDA QUESTIONS

QUESTION 1. What would be acceptable clinical study endpoints for devices that are intended to be therapeutic, that is, for devices intended to have indications for use such as:

A. a change in the appearance of cellulite

B. a temporary change in the appearance of cellulite

C. for body contouring

D. for body contouring through fat reduction

The panel agreed that **patient satisfaction, while important, is not the only measure and that more scientific endpoints should be used**. The panel did not deal specifically with indications, such as cellulite.

QUESTION 2. What measures of clinical improvement is appropriate, and how much is necessary? Is patient satisfaction alone sufficient, or should scientifically-validated evaluation scales be developed, possibly including masked evaluations? Should the treatment also have a clinical efficacy? For example, should body contouring/reduction in abdominal fat also show an improved health outcome? If clinical outcome is necessary, what specific measures of clinical improvement would be appropriate, and how large an improvement is necessary?

The panel agreed that **measures of clinical improvement are needed and necessary**, and treatment should have clinical efficacy, but they could not come up with specifics, saying that each device had different measurement requirements.

Panel comments included:

- *Panel chair Dr. LoCicero:* "Patient satisfaction is important but it is not the only measure and there is some potential for using a more scientific endpoint as an additional piece of information…They (companies) should not make claims to clinical improvement unless it's absolutely, certainly proven…If they make a claim, they have to prove it. A claim of health benefit would have to be proven if a (sponsor) wants a new indication."
- *New York dermatologist:* "Whatever the outcome might be…it has to be substantiated rigorously."
- *Plastic surgeon and epidemiologist:* "I'd take that claim off the table, but perhaps that's not my decision. But with respect to satisfaction as an outcome endpoint only, I think there has to be some measure of effectiveness from a natural change of contour. You can't use satisfaction alone, but if we do, we have to validate an instrument to do it."
- *Dr. McGrath, a plastic surgeon:* "It is important to substantiate a claim to prevent consumer fraud."

QUESTION 3. For devices intended for aesthetics (temporary change in appearance), should the treatment be so well understood that the user can pre-set the amount of change that will occur? For example, if the device is intended for eyebrow lift, should the amount of lift to be achieved be controlled and predictable before initiation of treatment?

The panel agreed that **device operators need to know *how* to operate their machines**, but panel members were divided as to whether some devices can pre-determine what amount of change will occur due to variabilities of patient anatomy. Several panel members suggested that device operators be able to tell patients what percentage of change was seen in clinical studies.

Panel comments included:

- *Panel chair:* "The way this is worded is a little tricky for me. It seems like there should be some control over what it is that you're trying to do. If it's quantifiable, like the amount of an eyebrow lift – I guess I'm going around in a circle. If the patient is unsatisfied after the treatment for effectiveness, that is an endpoint for me. If it's going to be a viable commercial procedure, there should be some verifiable, noticeable change to the patient."
- *FDA official:* "Should there be something quantifiable? The ability to predict is the panacea, but the issue we're after is should there be some kind of quantifiable measurement associated with these devices?"
- *Panel chair:* "Are you also asking if you press the button, do you get a predictable effect for each time it's used?"
- *FDA official:* "That's one of the embedded questions."
- *Another FDA official:* "I was thinking about lasers for LASIK. You represent the amount of corneal removal, and you get it. With these devices you can predict how much tissue you get a lesion in, but that doesn't always work out to the same amount of tightening…Are we seeing the physicians telling the patient how much change they're going to get from this amount of treatment? Is there are minimum amount we would require? Should they be able to tell the patient what they're going to see?"
- *Halpin, the industry representative:* "I think this is a very different situation from LASIK, where you have to have a computer help you do it. This is the opposite; you're using the expertise of the user to achieve cosmetic change which is individual for a patient and can't be standardized."
- *New York dermatologist:* "There are a lot of variables in a patient's health that will impact the outcome – what tissue response is, whether there is underlying disease, what medications they're on. That said, there should be guidelines here. The physician could say that 50% of individuals who have this treatment can achieve a 2 mm brow lift. It should be clinically relevant. A 1 mm change is not going to be clinically significant. And exposure to risk wouldn't be warranted in that situation. So, there should be some guidelines that show that the patient will achieve an outcome which will be at least equal to the following."
- *Plastic surgeon and epidemiologist:* "I think the device will be in someone's hands, not the physician, and they will depend on the programming of the device."
- *Another dermatologist:* "Every patient could be told the percentage of chance that it works, like less than 50% or 90% of some quantifiable data. I think also that part of the predictability and control is that it doesn't over act, so you don't have some patients come out with a startled look for days or weeks. So, within this control and predictability is the safety issue as well as not over exaggerating what the device does."
- *FDA:* "Should the operator then have some sort of summary of the clinical studies?"
- *Panel member:* "They will read the manual, but maybe there should be a mandatory handout to every patient, so each patient has the opportunity to read it."
- *Panel chair:* "We're dancing around the issue of training and qualifications. What would be appropriate in terms of guidance for the FDA when they're talking to sponsors?"
- *Industry rep:* "It's in the best interests of manufacturers to have operators who are appropriately trained and qualified to use their products. It's a very good idea and probably would help manufacturers help design control requirements."
- *Surgeon:* "I agree very strongly about training. Someone who knows how to operate a machine may not know how skin or anatomy works, and it's very important that they have the necessary training."
- *Dr. McGrath, a plastic surgeon:* "One thing that is becoming clearer to professional organizations is that the question of training is a complex issue…A lot of devices have the attachment that there must be training…What's going to happen when this goes away from educating the physician to educating someone who is not a health professional?"
- *Industry rep:* "The requirements are going to vary greatly on labeling. Certain requirements will be necessary to use this product. Those will be very different products. Over-the-counter (OTC) the requirements are going to be very different in terms of robustness of product and the ability of people to use it on themselves. But it will be very product-specific."
- *Dr. McGrath:* "For the FDA, then, the question is: Is training just a generic term left up to the manufacturers? Where are we with understanding whether people have acquired the skills to use these things?"

- *FDA:* "In general, the question is not something that we can ask, but in terms of requiring a particular training we usually ask the manufacturers to commit to training and tell us what that would be."
- *Panel chair:* "Should the operator of the device know what's under the hood and know the predictable change when they press the pedal?"
- *Dr. Olding, a plastic surgeon:* "It depends on the possibility for a complication rate. The more predictable, the less they have to know."
- *Plastic surgeon:* "I agree with that; it's a device-by-device issue."
- *Panel chair:* "There should be some predictable amount that the sponsor should be able to impart to the user, and the user needs to understand the device before stepping on the pedal."

QUESTION 4. What recommendations would you make regarding the FDA's review of those devices that present minimal risk and appear to have little or minimal tissue effect for indications such as body contouring or reduction in fat thickness or improvement in skin appearance?

Most panel members were unwilling to delve into this subject, although one dermatologist said that she saw many procedures that simply did not result in any quantitative change. As one panel member said, "The truth is in the beholder." Panel members generally **could not make any recommendations except to say that any claims must be verified**.

Panel comments included:

- *Panel chair Dr. LoCicero:* "Would snake oil fit in there? Or would it be a device?"
- *FDA:* "We're trying to distinguish between things that we know affect tissue and some of the LED-type devices that are being sold in Nordstrom and places like that which are apparently not doing any direct tissue effects that we see that are obvious. Those devices also are making medical claims, and if we have to review them, how do we go about doing that? Those devices where clearly we see tissue effect, histological change vs. the LED light sources being promoted for improving the appearance of the face, clearer skin, etc."
- *Dr. Walker, a dermatologist:* "(With) the low level light sources, even when first introduced…it wasn't clear what the histology was, what the endpoint was in terms of really reproducible effects, and that's probably true for these OTC devices. The truth is in the eye of the beholder, and I'm not certain there was enough science then or now to support the claim of a more youthful appearance. However, (it's) the person's own view if they feel that is true. It's somewhat of a snake oil effect, but it is hard to disprove or prove."
- *New York dermatologist:* "If we think of UV (ultraviolet light) salons, they are absolutely dangerous. The settings may not be carefully regulated, and these are things that we, as dermatologists, see, and eye protection and medications can affect this. Let alone the fact the UV is dangerous…Every device should have some quantifiable proof that it works and definite safety limitations. I'd like the FDA to define 'temporary' and give some percentage of efficacy."
- *Another dermatologist:* "I've never seen anyone achieve benefit from these low level light sources whatsoever except psychologically. They fulfill one of the claims used in cosmetics – the mind claim, it makes me feel better. That certainly is acceptable, but I don't think that fulfills our criteria here. (With) the so-called data I've seen on several of these devices, it's challenging to see any difference. If I can't see the difference before and after, I don't think there is a difference. I can't see the impact on a cellular level, but it took many years to see the impact of UV light on the skin. I'm concerned many years later we might find there is some kind of long-term impact, and that concerns me greatly. I don't think they should be on the market."
- *Panel chair Dr. LoCicero:* "It does a disservice to the public. There is a whole host of these things that cause cellular damage at some level. I don't think you can drop your guard on this…We are uniform that if it's a device that makes a change, that needs to be proven, shown. And there needs to be some science in evaluating it. Regardless of how minimal we think it is, safety is a concern."

What is "temporary"?

- *Dr. LoCicero:* "It's tough to figure out what the durability recommendations would be given the lack of information in all these categories. I don't know how to give a global suggestion given all the devices, etc. I'm at a loss for a universal guideline."
- *New York dermatologist:* "Every individual device should define the time they expect the treatment to be efficacious. If it's temporary, define the term 'temporary' specifically."
- *Dr. Olding, a plastic surgeon:* "I agree that for those products that are indicating a temporary effect, they have to be precisely defined. For permanent ones, with histological change, the histological level has to be defined. They have to be documented until they return to a stable milieu. For clinicians we often say we won't operate for nine months or a year because there is often collagen reformation during that year. I'd follow either out to a year or until there is demonstrable stability in the change that has occurred."

Dr. LoCicero, the panel chair, summed up the meeting: "We've provided a fair amount of discussion, particularly for the temporary-effect devices. There should be some evaluation for the FDA to see from the sponsor. We struggle with the issue of the permanent devices and when the evaluation should take place. And we can't come to a great conclusion about endpoints, maybe settling on some endpoint that is close in and then surveillance beyond that point."

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