Executive Summary

Dermal Filler Devices

Food and Drug Administration

Center for Devices and Radiological Health

Office of Device Evaluation

General and Plastic Surgery Devices Panel

Public Advisory Committee Meeting

November 18, 2008

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FDA General and Plastic Surgery Devices Panel

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I. Introduction - Focus of Panel Discussion

It has been over 20 years since the approval of the first dermal filler device, with the majority of the currently marketed dermal fillers approved in the last 10 years. The types of materials approved for dermal fillers vary from biologic to synthetic materials and absorbable to non-absorbable compounds. Some dermal filler formulations are available with lidocaine to reduce pain during injection.

Dermal filler devices are, in general, approved for injection into the mid to deep dermis for the correction of moderate to severe wrinkles and folds. Two injectable dermal fillers have been approved for restoration and/or correction of signs of facial fat loss (lipoatrophy) in patients with human immunodeficiency virus (HIV). Of these two devices, one is also approved for the general indication of correction of wrinkles. The panel discussion of November 18th, 2008 will be focused to the use of dermal fillers for correction of moderate to severe wrinkles, as this is the intended use that is more broadly applicable to the general population.

The clinical studies conducted by manufacturers to support the safety and effectiveness of each dermal filler device for FDA approval involved evaluation of device injection into nasolabial folds. In cases where lidocaine inclusive formulations were introduced following FDA approval of the dermal filler, separate clinical studies evaluating pain during injection were conducted. Nasolabial folds were considered representative of moderate to severe facial wrinkles and folds and thus data collected from these studies were accepted to support the approved indications for use for dermal fillers.

FDA has surveyed many uses of dermal fillers that go beyond the use of filling moderate to severe facial wrinkles. Available, published literature strongly suggests that dermal fillers are increasingly used to augment and contour tissues, in addition to improving the appearance of wrinkles. In light of this expanding use of dermal fillers, FDA recently published a consumer article in order to communicate FDA's understanding of the safe and effective use of dermal filler devices (http://www.fda.gov/consumer/updates/wrinklefillers062608.html).

With growing consumer demand, FDA expects the continued submission of premarket applications for dermal fillers for filling of wrinkles and possibly new indications for use such as augmenting and contouring of face and body. Therefore, FDA is interested in evaluating the post-market experience of these devices and using these data to determine if any improvements can be made to the pre-market approval study design, device labeling, and communication of post-market surveillance information collected by FDA on dermal filler devices. Questions developed by FDA to be posed to the panel in order to guide this discussion are provided in the section following this executive summary.

II. FDA Approved Dermal Fillers

1. Types of dermal fillers

The following table outlines the brand names and types of dermal fillers that have been FDA approved. The Summary of Safety and Effectiveness Data and labeling for each of these devices are also attached.

Table II.A. Approved Dermal Fillers

	Non-absorbable	**Absorbable**			
		Synthetic		Natural	
Major Component	Poly(methyl methacrylate) (PMMA) microspheres	Hydroxylapatite	Poly(L-lactic acid)	Hyaluronic Acid	Collagen
Brand Name *(Manufacturer)*	Artefill *(Artes Medical)*	Radiesse[#] *(Bioform Medical)*	Sculptra[*] *(Sanofi Aventis Pharmaceutical)*	Restylane, Perlane *(Medicis Aesthetics Holdings)* Hylaform, Hylaform Plus *(Genzyme Biosurgery)*	Zyderm, Zyplast *(Allergan)* Cosmoderm, Cosmoplast *(Allergan)*

				Juvederm 30, Juvederm 30HV, Juvederm 24HV *(Allergan)* Elevess *(Anika Therapeutics)*	Evolence *(Colbar Lifesciences)*

[#] *Indicated for use for both correction of moderate to severe facial folds and wrinkles and for correction of the signs of lipoatrophy in people with HIV*
[*] *Indicated only for use for correction of the signs of lipoatrophy in people with HIV*

Poly(methyl methacrylate)

ArteFill

Artes Medical USA, Inc. (P020012; Approved 10/27/2006)

Indications for Use: ArteFill is indicated for the correction of nasolabial folds

Device Description: ArteFill is an implant composed of non-resorbable polymethylmethacrylate (PMMA) microspheres, 30-50 microns in diameter, suspended in a water-based carrier gel composed of 3.5% bovine collagen, 92.6% buffered, isotonic water for injection, 0.3% lidocaine HCl, 2.7% phosphate buffer, and 0.9% sodium chloride.

Hydroxylapatite

Radiesse

Bioform Medical, Inc. (P050052; Approved 12/22/2006)

Indications for Use: Radiesse is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Device Description: Radiesse is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite (CaHA) suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. Radiesse (1.3 cc and 0.3 cc) has a CaHA particle size range of 25-45 microns and should be injected with a 25-27 gauge needle.

Radiesse

(P050037; Approved 12/23/2006)

Indications for Use: Radiesse is indicated for subdermal implantation for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

Device Description: Radiesse is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite (CaHA) suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. Radiesse (1.3 cc and 0.3 cc) has a CaHA particle size range of 25-45 microns and should be injected with a 25-27 gauge needle.

<u>Poly(L-lactic acid)</u>

Sculptra

Sanofi Aventis Pharmaceuticals, Inc. (P030050; Approved 08/03/2004)

Indications for Use: Sculptra is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with or receiving treatment for human immunodeficiency virus.
Device Description: Sculptra is an injectable poly-L-lactic acid implant in the form of a sterile lyophilized cake. Sculptra contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. Sculptra is reconstituted prior to use by the addition of Sterile Water for Injections, USP (SWFI) to form a sterile non-pyrogenic suspension.

Hyaluronic Acid

Hylaform, Hylaform Plus, Captique

Genzyme Biosurgery (P030032; Approved 04/22/2004)
Indications for Use: Hylaform, Hylaform Plus, and Captique are indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
Device Description: Hylaform and Captique are injectable sterile, non-pyrogenic, viscoelastic, clear colorless gels implants composed of cross-linked hyaluronan made from rooster combs and gram positive bacteria, respectively.

Restylane Injectable Gel, Perlane Injectable Gel

Medicis Aesthetics Holdings, Inc. (P040024; Approved 03/25/2005)
Indications for Use: Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Perlane is

indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Device Description: Restylane consists of stabilized, hyaluronic acid (HA) generated by streptococcal bacteria and formulated to a concentration of 20 mg/ml, suspended in a physiological buffer pH 7. Restylane is a transparent, viscous and sterile gel, supplied in a disposable glass syringe. The syringe is packed in a blister together with a sterile 30 G needle. The HA has a molecular weight of about 1 million and is stabilized by adding a minimum amount of BDDE (1,4-butanediol diglycidyl ether) to allow formation of a 3-dimensional HA molecular network (gel). Perlane is a sterile gel of hyaluronic acid generated by Streptococcus species of bacteria, chemically cross-linked with BDDE, stabilized and suspended in phosphate buffered saline at pH = 7 and concentration of 20 mg/ml. The largest fraction of gel particles size is between 940 and 1090 microns.

Juvederm Gel Implants (Juvederm 30, Juvederm 24HV, Juvederm 30HV)

Allergan (P050047; Approved 06/02/2006)

Indications for Use: Juvederm 30, Juvederm 24HV, and Juvederm 30HV are injectable gels indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

Device Description: JUVEDERM injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant. JUVEDERM consists of crosslinked hyaluronic acid (HA) formulated to a concentration of 22-26 mg/mL, suspended in a physiological buffer. The HA in JUVEDERM is produced by Streptococcus equi bacteria. The HA used in JUVEDERM has a molecular weight of approximately 2.5 million Daltons and is

crosslinked by adding a minimum amount of BDDE to form a 3-dimensional HA gel. JUVEDERM is available in three formulations (30, 24HV and 30HV) and is supplied in pre-filled disposable syringes. Juvederm 30 HV is a more highly crosslinked robust formulation, injected using a 27G needle for volumizing and correction of deeper folds and wrinkles. Juvederm 24HV is a highly crosslinked formulation that can be injected using a 30 G needle for more versatility in contouring and volumizing of facial wrinkles and folds. Juvederm 30 is a highly crosslinked formulation, injected using a 27G needle, for subtle correction of facial wrinkles and folds.

Elevess

Anika Therapeutics, Inc. (P050033; Approved 12/20/2006)

Indications for Use: Elevess or Cosmetic Tissue Augmentation Product (CTA) is indicated for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

Device Description: CTA is a sterile, non-pyrogenic gel implant, composed of hyaluronan produced by Streptococcus equi (bacterial fermentation) that is crosslinked and suspended in a buffer solution at a concentration 28 mg/ml. CTA CONTAINS 0.3% lidocaine HCl. The finished product is provided in a pre-filled glass syringe at a volume of 1ml, co-packaged with two 30G x ½ inch hypodermic needles.

Collagen

Evolence Porcine Collagen Dermal Filler

Colbar LifeScience (P070013; Approved 06/27/2008)

Indications for Use: Evolence Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

Device Description: Evolence Collagen Filler is a sterile, non-pyrogenic device stable at physiological pH that is yellowish, homogeneous, opaque gel, prepackaged in a syringe. It is composed of a 35 mg/ml (± 5 mg/ml) biodegradable Type I fibrillar porcine collagen crosslinked using D-ribose suspended in phosphate buffered saline (PBS). Various antigenic portions of the collagen molecule have been removed.

Cosmoderm, Cosmoplast

Allergan (P800022, Supplement 50; Approved 03/11/2003)

Indications for Use: CosmoDerm™ 1 Human-Based Collagen and CosmoDerm™ 2 Human-Based Collagen are injected into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars. CosmoPlast™ Human-Based Collagen is injected into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

Device Description: CosmoDerm and CosmoPlast Human-Based Collagen implants are sterile devices composed of highly purified human-based collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine. CosmoDerm Human-Based Collagen implants are available in two forms: CosmoDerm™ 1 Human-Based Collagen and CosmoDerm™ 2 Human-Based Collagen. CosmoDerm™ 2 Human-Based Collagen implant contains almost twice the collagen concentration of CosmoDerm™ 1 Human-Based Collagen. CosmoPlast™ Human-Based Collagen is a sterile device composed of highly purified human-based collagen that is crosslinked with glutaraldehyde, and dispersed in phosphate-buffered

physiological saline containing 0.3% lidocaine. CosmoDerm and CosmoPlast Human-Based Collagen implants contain collagen purified from human fibroblast cell culture. The cell line used for collagen production is qualified by extensive testing for viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity.

Zyderm Collagen Implant, Zyplast

Allergan (P800022; Approved 07/22/1981)

Indications for Use: Zyderm is indicated for the correction of contour deformities of the dermis in non-weight bearing areas. Zyplast is indicated for the correction of contour deficiencies of soft tissue.

Device Description: Zyderm collagen implant is a sterile device composed of highly purified bovine dermal collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine. Zyderm collagen implant is available in 2 forms: Zyderm 1 collagen implant and Zyderm 2 collagen implant. Zyderm 2 collagen implant contains almost twice the collagen concentration of Zyderm 1 collagen implant. Zyplast collagen implant is a sterile device composed of highly purified bovine dermal collagen that is lightly crosslinked with glutaraldehyde and dispersed in a phosphate-buffered physiological saline containing 0.3% lidocaine.

2. General Labeling Information for Dermal Fillers

Indications for Use

In general, dermal fillers are indicated for injection into mid to deep dermis for the correction of moderate to severe wrinkles and folds. Some devices have limited indications for use such as:

- correction of nasolabial folds (contraindicated for injection in areas other than nasolabial folds); or
- restoration and/or correction of signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

Some dermal fillers are also indicated for use to fill areas of acne scars.

Contraindications for Use

All dermal fillers are contraindicated for patients with

- known sensitivities to the filler material; and
- history of severe allergy or anaphylaxis; and
- bleeding disorders.

Warnings and Precautions

In general, the following warnings and precautions are applicable to all dermal fillers. There are additional warnings that may be device specific, such as those related to device material composition.

- 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
- The safety and effectiveness of device injection for lip augmentation had not been established
- Injection into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes
- The safety in patients susceptible to keloid formation, hyperpigmentation and hypertrophic scarring has not been established
- Long term safety and effectiveness of the device beyond duration of clinical study have not been investigated

III. Evaluation of Dermal Filler Use in Subjects with Fitzpatrick Skin Types IV-VI

1. Summary of Post-Approval Studies

Introduction

Since 2003, the Food and Drug Administration (FDA) has approved 9 dermal filler devices with the condition of approval that the sponsor conduct a post-approval study (PAS) in the population with Fitzpatrick skin types IV-VI. The purpose of these post-approval studies was to assess the safety of dermal filler use in subjects with Fitzpatrick Skin Types IV-VI as this population was under-represented in the pre-market clinical studies. The post-approval studies for 3 devices are currently ongoing, and since these studies are still recruiting subjects, manufacturers have yet to report any data to FDA. Three post-approval studies for the other 6 devices have been conducted and completed. The following includes a brief summary of the completed post-approval studies.

Post-Approval Study Design

The major component of the dermal filler devices in these three studies is hyaluronic acid from various sources such as bacterial or avian or synthetic calcium hydroxylapatite. The indication for these devices consists of subdermal implantation for correction of moderate to severe facial wrinkles and folds. These post-approval studies were completed between 2005 and 2007. The primary objective of all studies was to evaluate the safety of device use in the population with Fitzpatrick skin types IV-VI particularly with respect to certain adverse events including keloid formation, pigmentation changes, hypertrophic scarring, and hypersensitivity. Table 1

summarizes the design of the studies. The study population consisted of subjects with Fitzpatrick skin types IV-VI.

These were open-label studies with no comparison group. All studies recruited new subjects. Two studies offered only one injection to subjects and the third study offered a touch-up injection two weeks after the first injection. One study followed a split-face design in which two devices from the same product line were examined with a single device applied to each side of the face. Adverse event data were collected for each subject at the post-injection study visits. The follow-up period was between 24-26 weeks.

Table III.A. Summary of Study Designs

	PAS 1	**PAS 2**	**PAS 3**
No. devices evaluated	1	3	2
Sample size	100	119	150
No. injections	1	1	1 or 2
Injection sites	Nasolabial folds	Nasolabial folds	Nasolabial folds and oral commissures
Study visits after injection	3 and 6 months	2, 4, 12, and 24 weeks	3 days, 2, 6, 12, and 24 weeks
Patient diary	No	No	Yes
Effectiveness data	No	No	Yes
Hypersensitivity	No	Yes	Yes
No. of subjects with each Fitzpatrick skin type	IV=24 (24%) V=35 (35%) VI=41 (41%)	IV=32 (27%) V=56 (47%) VI=31 (26%)	IV=44 (29%) V=68 (45%) VI=38 (26%)

Post-Approval Study Data

Table III.B. Primary adverse events

Adverse Event	Incidence
Hypersensitivity	0
Keloid formation	0
Hypertrophic scarring	0 (1)
Hyperpigmentation	20 (6)
Hypopigmentation	1 (2)
Nodule/mass formation	10

**The number of events provided in parentheses are those reported as not related to device/procedure*

No keloid formation was observed in these post-approval studies. PAS reported 17 hyperpigmentation events as related to device/procedure and 6 hyperpigmentation events as unrelated to device/procedure 2 of which occurred on the lips. There were 1 hypopigmentation event as related to device/procedure and 2 additional hypopigmentation events as unrelated to device/procedure. There was 1 hypertrophic scarring event as unrelated to device/procedure. Ten occurrences of mass/nodule formation were reported. The duration of nodule/mass formation events reported was 70-85 days.

PAS Design Limitations

The three completed studies carried the following design limitations. Data collected from these studies should be evaluated with these limitations in mind. The studies are descriptive and as such may carry certain systematic errors and bias.

- These studies were not sufficiently powered to detect adverse events with a low rate of incidence in the study population. Two studies evaluated more than one version of a device so the power may be reduced further.

- Two of the studies offered injection of dermal filler at one visit which may not reflect real-world use of these devices where multiple visits may be required to maintain optimal cosmetic results.

- None of the studies included a control group. The intent was to compare the data collected through the post-approval studies with that of the premarket studies in terms of the adverse events. Due to differences in the study design and study populations, direct comparison between the two data sets may be difficult.

- Subject and investigator bias may be present as is the case with any open-label clinical study.

- Short term adverse events may have been under-reported in studies where patient diaries were not provided.

- Subjects were followed up to a 6-month period. Therefore, these studies did not capture adverse events that may have developed past this follow-up period.

2. Summary of Available Literature and Statistics

Although statistics on the incidence and prevalence of keloid formation, pigmentation changes, and hypertrophic scarring in people with darker skin after the administration of soft tissue dermal fillers are not available, there is some anecdotal evidence about the incidence of some of these events in the darker skin population in general (not related to these devices). English and Shenefelt[(1)] reported that an incidence of keloids between 4.5% and 16% have been reported in a predominantly darker skin population, and up to 16% in random samplings of dark skinned Africans. The incidence of hypertrophic scars is possibly higher than that of keloids, but good data are lacking.

In order to put in perspective the prevalence of use of soft tissue dermal fillers among non-Caucasian populations, the following statistics are provided.

The National Ambulatory Medical Care Survey (NAMCS) is a nationally representative survey of office-based physicians although not including federal and university-based clinics. It is conducted by the National Center for Health Statistics. The survey captures information on procedures performed in the physician office setting but does not reflect inpatient or ambulatory surgical center care. A study[(2)] using NAMCS reported that from 1995 to 2003, soft tissue fillers constituted 18.4% (over 2.5 million procedures) of office-based cosmetic procedure visits. Ninety percent of office-based cosmetic procedures were performed on Caucasian patients and 10% on non-Caucasian patients. The American Society of Plastic Surgeons in its 2007 Cosmetic Demographics by Patient Ethnicity[(3)] reported that injectable fillers are one of the three most

commonly-requested and minimally-invasive procedures among African-Americans, Asian-Americans, and Hispanics who are seeking cosmetic procedures.

3. References

1. English RS, Shenefelt PD. Keloids and hypertrophic scars. *Dermatologic Surgery* 1999; 25:631-638.
2. Housman TS, Hancox JG, et al. What specialties perform the most common outpatient cosmetic procedures in the United States? *Dermatologic Surgery* 2008; 34:1-8.
3. American Society of Plastic Surgeons. 2008 Report of the 2007 Statistics National Clearinghouse of Plastic Surgery Statistics. http://www.plasticsurgery.org/media/statistics. Accessed on 9/24/08.

IV. Post-Market Evaluation of Adverse Events Reported to FDA

1. Introduction

The purpose of this section is to provide a brief review of adverse event reports associated with the use of all injectable dermal filler devices manufactured by a number of different companies. The data presented in this analysis covers Medical Device Reports (MDRs) received by FDA up to September 2008.

2. Methods

The Manufacturer and User Facility Device Experience (MAUDE) database was searched using two search criteria: Product Code LMH (Dermal filler, injectable, for aesthetic use), and date report received (for reports for the last 6 years, from Jan 1, 2003 through Sep 20, 2008). The search generated 1032 reports. All reports were individually reviewed unrelated and duplicate reports were removed, leaving a total of 930 reports. After event narratives were reviewed, reports were classified by type of adverse event and site of injection, and the frequency of the adverse events was tabulated.

<u>Limitations for data analysis</u>

Several limitations which were identified during the reports review process are listed below:

- Many reports indicated that the patient received multiple injections at once in different sites

but did not specify which site was involved in the adverse events reported.

- A number of reports indicated that the patient received series of injections but did not specify the time intervals between the injections, and did not mention which one in the course of injections triggered the adverse events.

- Some reports indicated that the patient received multiple brands of dermal implants but did not mention which adverse events occurred at which brand's injection site.

- Many reports did not specify site of injection or used general terms such as "face" or "treatment site".

- Onset of adverse events was missing in many reports.

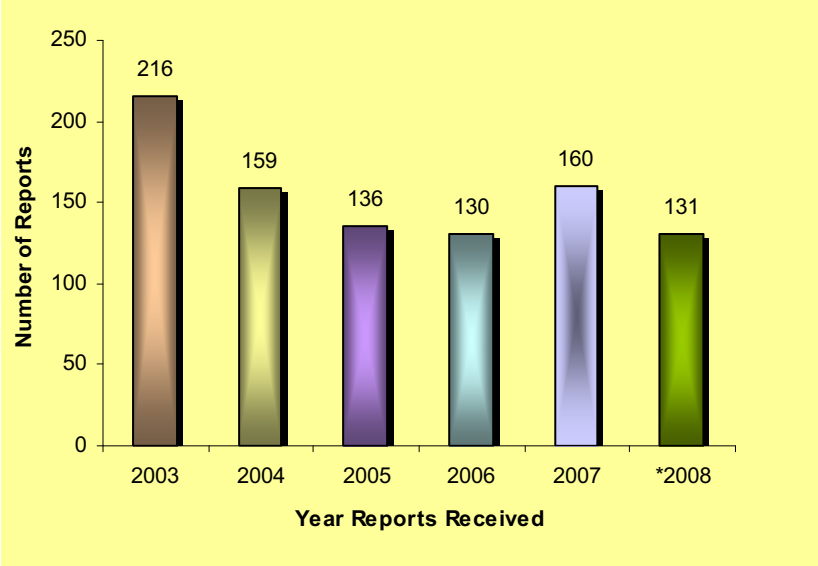
- Different reporters used different terminology for sites of injection and adverse events, or used non specific terms such as lumps, bumps, mass, and so on.

- Direct association of the adverse events with the product injected is not explicitly identified in majority of reports' narratives.

3. Results

The 930 reports represent 930 unique events. The number of reports and date reports received is presented in Figure 1.

Figure 1. Number of Reports by Year Received



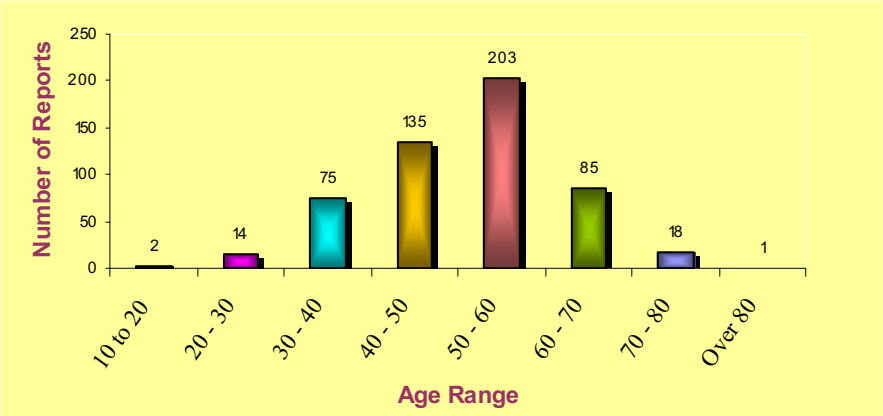
*Note: Number of reports up to September 20.

Reporting sources included 877 manufacturers and 53 voluntary reports. Reports' country of origin was specified in 674 reports: 739 from US, 135 from outside US. Eighteen countries, including a number of European countries, Australia, Japan, China, South Africa and Brazil, were among the foreign countries reporting, with Australia, France, and United Kingdom reporting the most.

Patient Demographic

Gender was reported in 804 reports; 763 females and 41 males. Age was reported in 533 reports and ranged from 17 to 86 years. The age distribution is presented in figure 2 below.

Figure 2. Number of Reports by Patients' Age (n=804)



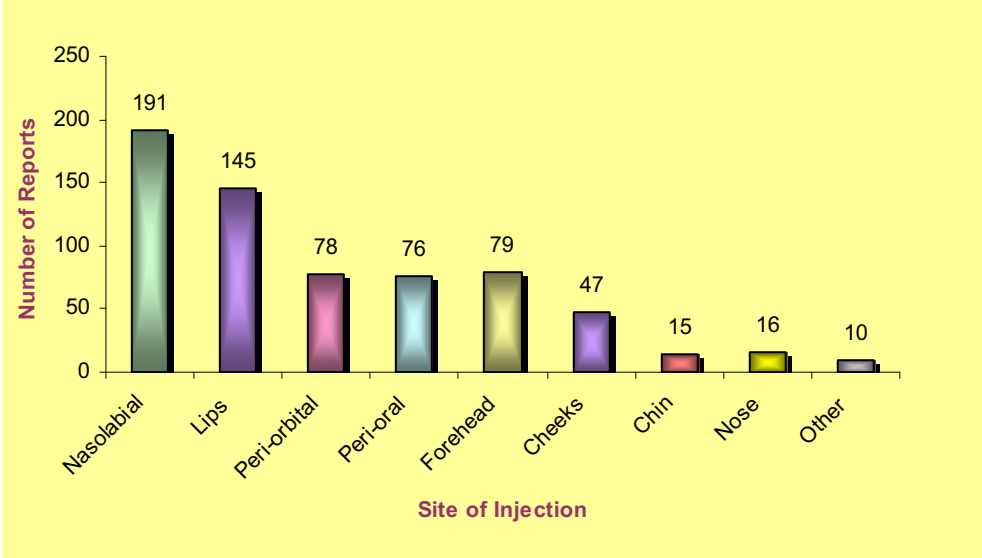
Sites of injections

Site of injections were specified in 536 reports, with site of injection referred to generally as "face" in 16 reports, and 378 reports did not mention the site of injection. In 536 reports that specified site of injection, 345 reports indicated only one site of injection and 191 reports indicated more than one site of injections.

Site of injections were grouped into 9 categories of terms most often used for the location of injections: 1) Nasolabial, 2) Lips --including vermillion border, and lips vertical line, 3) Peri-orbital--including eyelids, and under eyes, 4) Peri-oral--including marionette line, and around mouth, 5) Forehead--including glabellar crease and temple area, 6) Cheeks, 7) Chin, 8) Nose,

and 9) Other sites--including hands, forearm, ear lobe, nipple, foot, and neck. Figure 3 demonstrates the frequency of each injection site category in 536 reports that identified site of injections.

Figure 3. Number of Reports by Injection Site (n=536)



Notes: 1-Total number of reports in this table is not equal to the number of MDRs because many reports indicated multiple site of injections in a single patient.
2- Other sites includes (4 hands, 2 ear lobe, 1 nipple, 1 foot, 1 neck, and 1 forearm)

Adverse events

Types of events in 930 reports were: 0 deaths, 823 injuries (88%), 93 malfunctions (10%), and 14 reports identified as "Other" (2%). Each type of event is discussed in the following sections. Figure 3 demonstrates the percentile rate of type of events.

Injuries

Adverse events were grouped into 13 categories identified by frequently used terms describing similar adverse events. Furthermore, the frequency of adverse events was calculated by counting

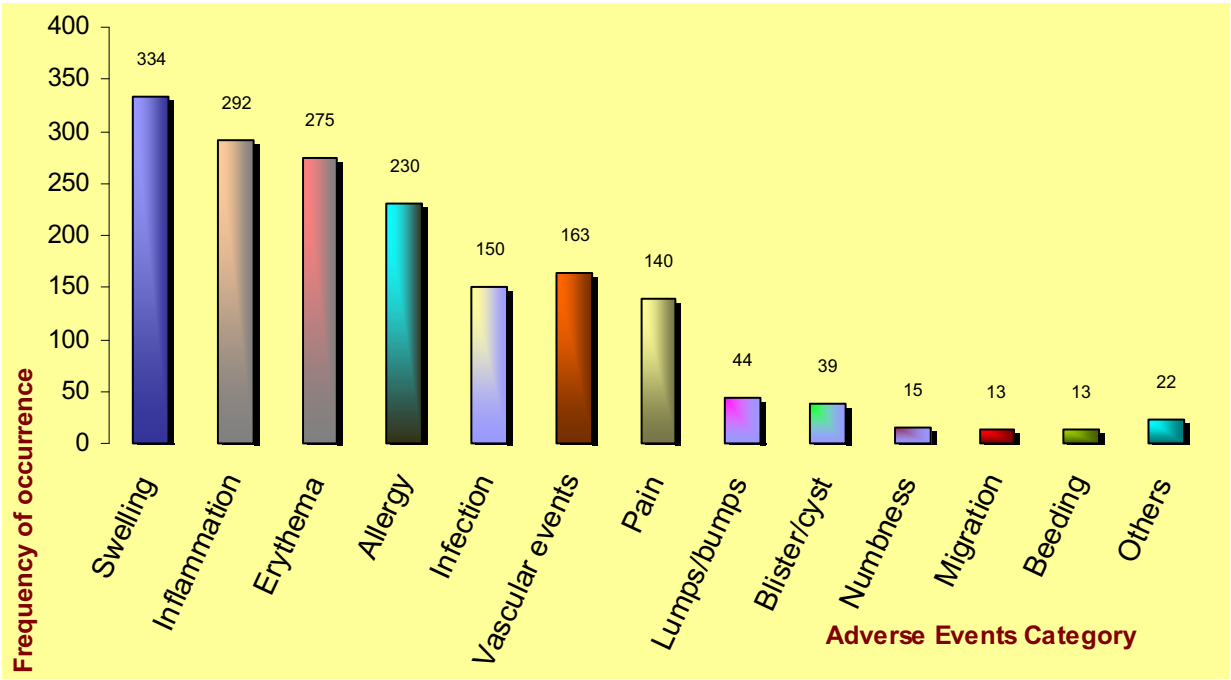
each and every term used to describe the adverse event in the reports' narratives. For example, if the report's narrative indicated allergic reaction, hypersensitivity, edema, and nodule formation in a single patient, all of the four adverse events were calculated for that report. Terms used to describe each category of adverse events follows.

1. Allergic reaction: Included the term allergic reaction and hypersensitivity, severe systemic reaction, swelling of the tongue and difficulty breathing, anaphylactic shock, hives, pruritis, itching, rash, urticaria, angioedema, and hyperpigmentation.
2. Swelling: Included the term swelling and edema.
3. Inflammatory reaction: Included nodule formation, granulation, induration, papules, cold sores, herpes and arthritis flare up.
4. Erythema: Included the term erythema and redness.
5. Infection: Included the terms infection, abscess, cellulitis, postulate, uveitis, conjunctivitis, pus and drainage.
6. Vascular events: Included bruising, bleeding, hematoma, necrosis and scars, blanching and discoloration, and ischemia
7. Pain: Include pain at the site of injection, muscle ache, and head ache.
8. Blisters and cysts.
9. Non-specific masses: Included lumps and bumps.
10. Beading: Included collection or clump of the implant under skin.
11. Numbness: Included the term numbness, paresthesia, and palsy.
12. Migration: Included moving of the implant from original site of injection to other sites.

13. Others: Included all other adverse events with occurrence frequency of less than ten such as Blurred vision, disfigurement, overcorrection, retained foreign body, fainting, tear duct obstruction and soreness, and heart attack.

Figure 4 demonstrates the frequency of occurrence of adverse events by the category of events.

Figure 4. Frequency of Adverse Event Occurrence by Category of Event



Note: A large number of reports indicated multiple adverse events in one patient, therefore, the number of adverse events exceeds the total number of injury reports.

Malfunction reports

Of the 93 malfunction reports, 90 were related to syringe luer lock problems and needle disengagement. Reports indicated that during the injection the needle was clogged and when the users tried to forcefully push the product through the needle, it disengaged, and dermal filler

splashed on the patient or the user. Three of 93 malfunction reports indicated breakage of the syringe, one caused a patient skin cut and another report indicated a cut on the physician's finger.

Reports identified as "Other"

Reports identified as "Other" indicated no patient adverse event as a result of dermal filler injection. Five of 14 reports were submitted by manufacturers and 9 were voluntary reports. Two of manufacturers' reports indicated user exposure to HIV patients' blood and body fluid while injecting the product, one reported the needle broke during injection and a small broken piece remained in the patient, one indicated wrong product was injected with no resulting adverse event, and one reported unspecified patient injury as a result of tools malfunction.

Of the 9 voluntary reports, 2 complained about lack of implant's effect, one reporter complained of a physician who is using an unapproved injectable dermal implant. One reporter complained of a manufacturer who refuses to disclose the side effects of the products. Five of the 9 voluntary reporters were from physicians who expressed concerns about the safety of some of injectable dermal implants.

Treatment of adverse events

Of the 823 injuries reports, 638 indicated that patients required treatment with medication. Medications ranged from topical application of steroid cream to multiple courses of oral antibiotics, topical steroids, anti-inflammatory or antihistamine drugs, and intra-lesion steroid injections. Ninety-four of 823 reports indicated surgical intervention, 44 of which were among the patients who received drug therapy as

well. Surgical procedures ranged from opening an abscess for drainage of pus, excision of nodules, to biopsy of the lesions.

Nineteen reports indicated patients' emergency room admission for immediate medical attention due to severe hypersensitivity reactions such as swollen tongue, difficulty breathing and anaphylactic shock. Twelve patients required hospitalization for extended IV antibiotic therapy and close monitoring. Three patients were monitored for an extended period of time in the clinic. One-hundred thirty-five reports did not specify treatment of adverse events.

4. Conclusions

- As reflected in Figure 3, the majority of dermal implant reports note injection in sites other than nasolabial fold, the indication of use for most of them.

- While many of reported adverse events, such as minor swelling and erythema, are expected problems and are specified in the labeling of the products, there are a numbers of adverse events that are serious and unexpected such as facial, lip, and eye palsy, disfigurement, retina vascular occlusion, as well as rare but life-threatening events such as severe allergic reactions and anaphylactic shock.

- Some of the common adverse events that are expected to occur shortly after injection and resolve quickly, have delayed onset and/or remain for a long period of time and turn into a more serious problems.

- A number of reports' narrative implies that the allergic reactions occurred after patients had their second or third injection.

- A number of reports' narrative implies that the injections of dermal implants are performed by untrained personnel or in settings other than health clinics or doctors offices.

- Analysis of the data should be viewed in light of the limitations mentioned previously.

V. Current clinical study designs for pre-market approval of dermal fillers

This section provides a summary of the range of parameters that have been utilized in clinical study design to collect data to support pre-market approval of dermal filler devices. For details on safety and effectiveness findings of these clinical studies, please review the attached summaries of safety and effectiveness data (SSED) provided for approved dermal fillers.

1. Clinical trial outline for dermal filler products used to treat facial wrinkles and folds

Study Protocol

From 2002-2007, manufacturers of dermal filler devices demonstrated their safety and effectiveness using predominantly randomized, controlled, multi-center clinical trials. Control designs included split face and standard design where one cohort of patients received the control device and the other cohort received the study device. Masking varied from:

1. Subjects who were either fully masked or partially masked.
2. Investigators who were either fully masked or unmasked.
3. Photographic review Panels that were always masked and used photographs.

Evaluation of treatment results ranged from live assessment (by the investigator) to photographic assessment (by the panel) using modified Fitzpatrick Wrinkle Scales (MFWS) or 6 point validated wrinkle severity scales.

Study Purpose

The studies were intended to evaluate the safety and effectiveness of study devices when used as a dermal filler in the nasolabial folds, moderate to severe facial wrinkles, facial folds and wrinkles (nasolabial folds and oral commissures) or correction of soft tissue contour deficiencies.

Treatment Plans

Injection depths varied from subdermis, deep or mid dermis. The linear threading technique, serial punctual injections (or a combination of the two) or tunnelling was used. Regarding pain management, physicians were either advised to assess the patient's need for pain management, use the standard of care, or manage pain during and after injection with topical or injectable anesthesia. Alternatively, in some studies, no instructions were given regarding pain management.

Sample Sizes

117-191 subjects were enrolled in these studies and 115-185 subjects completed these studies.

Endpoints

Primary endpoints included:

- The correction of the nasolabial folds as compared to the control, as determined by blinded evaluating investigators' (BEI's) live evaluation of the nasolabial fold (NLF)

severity score (utilizing MFWS or Facial fold assessment scale FFA) at the 6-month post-optimal cosmetic result (OCR) visit; the statistical objective was to demonstrate non-inferiority of the study device to control.

- Ability to correct nasolabial folds at 3 months in comparison to the control material as determined by an independent panel of masked dermatologists through photographic assessment.
- The Lemperle Rating Scale (LRS) score of wrinkle severity at 3 months after the last touch-up via masked, photographic assessments by 3 board certified physicians; a change in LRS of one unit was considered clinically significant.
- (Independent Expert Reviewer) NLF severity score over the post-treatment follow-up period.

Secondary endpoints included:

- Subject satisfaction (utilizing global improvement assessment (GIA)) with the overall treatment response; measurements of anti-porcine collagen antibodies and comparison of total volume of study device injected to the NLF to achieve OCR vs the study control.
- The investigator's visual assessment of each patient's nasolabial folds using the 6-point grading scale, and a qualitative assessment of the level of correction by the investigator and by the patient.
- Masked evaluators assessment of wrinkle severity 6 months after treatment combined with the volume of material injected.
- Subject's and the Investigator's live NLF severity assessments at 2, 4, and 6 months.
- Number of treatment sessions to achieve optimal cosmesis.

- Masked evaluator LRS at 1- and 4-months; subject LRS at 1-, 4- and 6-months; proportion of nasolabial folds returning to baseline at 6-months;

Safety endpoints included:

Safety was evaluated by comparing the incidence and severity of local and systemic adverse events reported by the treating investigator from the pretreatment skin testing through the 6-month post-OCR visit and by comparing the incidence and severity of clinical events in the 12 months after treatment completion.

Clinical site distribution

Most large scale studies designed to support PMA approval were performed in 4 to 10 clinical centers. The majority of the clinical sites were within the United States.

Study Demographics

Patients enrolled in large scale studies designed to support approval were generally aged 30 -77 years old (i.e., mean ages ranged from 52 – 56 years old). Subjects were predominately female (i.e., range 90 – 94%) and Caucasian (i.e., range 72% - 93%). With few exceptions, studies enrolled low numbers of subjects with Fitzpatrick skin types IV – VI, (i.e., 4-10%).

Study entry criteria prohibited enrollment when there was evidence of an existing immune response against the study device material components, a history of bleeding disorders or connective tissue disease, pregnancy, or if a patient was unwilling to forego other facial

treatments (e.g. alpha hydroxy agents, botulinum toxin type A, microdermabrasion or retinoic acid) during the study. Most studies also excluded patients with current or recent: 1) soft tissue facial augmentation, 2) immunosuppressive therapy, 3) chemotherapy, 4) systemic corticosteroids, 5) anticoagulant therapy, or 6) the use of other investigational products.

Activities at each visit

Pretreatment:

In addition to reviewing entry criteria, conducting a physical exam and collecting medication and medical histories, the pretreatment visit included a baseline assessment of wrinkle severity which was performed by investigator alone, investigator and independent expert reviewer or investigator and independent expert reviewer with subject assessment. When immune response evaluation was planned, (i.e., studies of collagen or hyaluronic acid devices), pre-baseline serum samples were collected. Such assessments were generally performed 1-4 weeks prior to treatment.

Treatment visit:

Immediately after device implantation, patients were monitored for adverse outcomes. Treating physician and subject evaluations of cosmetic outcomes were also performed. After each injection session, injection technique (e.g., serial puncture, linear threading or both), device volume and anesthetic use were generally recorded. Photographic records were generally collected at all study visits and when protocol dictated, on-site masked evaluations of wrinkle severity were performed.

Short Term Follow-up:

In most studies, subjects were contacted by phone or evaluated at a clinic visit 72 hours after treatment to determine the incidence, severity and type of adverse outcomes resulting from device injection. Subjects also generally completed a post-injection diary that recorded injection site reactions occurring during the first 14 days after treatment. Two weeks after the initial treatment, subjects returned to the clinic for evaluation of wrinkle severity and adverse events. Between one to three touch-up treatments were performed if optimal cosmetic correction was not achieved.

Longer term Follow-up:

The frequency and duration of clinical studies varied depending on the composition of the dermal filler, the proposed primary effectiveness endpoint and the anticipated duration of product implantation. Frequently, study visits occurred at 1, 3, 6, 9 and 12 months after the last injection. At these visits, the incidence, severity, duration and type of adverse events were recorded. Product effectiveness data (e.g., wrinkle severity, global aesthetic improvement, treating investigator and/or subject satisfaction) were determined via masked evaluator, treating physician and subjects as identified in the protocol. Serum samples for humoral response assessment were generally collected at 1 and 6 months post treatment.

VI. Clinical Study Design in Support of New Indications for Use for Dermal Fillers

Most dermal fillers are approved for use to correct and fill moderate to severe wrinkles. A survey of published literature and internet content reflects the use of dermal fillers for augmentation and contouring areas of the face and body in addition to filling of facial wrinkles and folds. Some commonly reported uses for aesthetic improvement are:

- lip augmentation,
- contouring of the chin,
- contouring of the nose,
- cheek augmentation, and
- hand volume augmentation.

Several publications that are representative of the literature and that are available for the above listed procedures are provided as part of this executive summary.

With growing consumer demand, FDA expects the continued submission of pre-market applications for dermal fillers for the current indication of filling of wrinkles and possibly for new indications that involve tissue augmentation and contouring of the face and body. The previous section described some general parameters that have been used in the design of clinical studies to collect safety and effectiveness data to support pre-market approval of dermal fillers for injection into mid to deep dermis for the correction of moderate to severe wrinkles and folds. Data collected from these clinical studies may provide some baseline information regarding the safety and effectiveness of dermal fillers for new indications. However, these new indications

may raise new safety and effectiveness questions which may need to be addressed in new clinical studies. Tissue augmentation and contouring may introduce new risks related to injection site (e.g. proximity to bone, nerves, and vessels, thickness of dermal and sub-dermal layers, and tolerance to swelling), amount of filler material used, and frequency of injection needed to produce optimal results. For some injection sites, one may need to consider the effect of dermal filler material on tissue function, such as sensation or dynamic range of mobility. Device migration may itself present as a significant risk if the device is injected in a site where the tissue space is less confined and where the device may be subject to movement.

Consequently, FDA expects that clinical study designs in support of new indications for use for dermal fillers may require consideration of study design parameters that are different from past dermal filler clinical studies. Study considerations would include items such as the role of a control arm in these studies, the type of controls to be used, and measurement of treatment effectiveness.

The type of control to be used in these studies may be current standard of care, if one exists, or the use of pre-injection, baseline data. The use of a control device will be important to assess both safety and effectiveness endpoints. There may be injection related risks. The ability to blind the subject to treatment and have a more unbiased assessment of treatment will require the selection of an appropriate control device.

In many of the applications for tissue augmentation and contouring, determination of device effectiveness will include aesthetic improvement, a consideration that may be highly subjective

to individual preference. Judgement of improvement in aesthetic appearance of an individual may be dependent on existing facial structure, age, ethnicity, and culture. The outcome of a pleasing aesthetic appearance after treatment may be difficult to parse into a measure that can be quantified on a validated scale or provide statistically significant data.

Study duration may also need to be varied depending on the injection site and type of augmentation and contouring. In some cases, the patient may need to be injected with small to moderate volumes of dermal filler in several successive treatments. The volume of injection material may also require long term studies to assess durability of material and total residence time. It may also be the case that the first treatment with dermal filler to augment or contour tissue will significantly alter the tissue physiology or produce sufficient scarring to result in unpredictable outcomes for repeat treatment.

Ideally, these clinical studies will be designed to collect data that can help determine the risk to benefit ratio of dermal filler use for a given indication. There may be new challenges to clinical study design of dermal filler devices for tissue augmentation and face and body recontouring. This advisory panel meeting will serve as a public forum for discussion of the above stated considerations regarding basic clinical study parameters within the context of dermal filler device use for aesthetic improvement.