FDA Executive Summary
General Issues Panel Meeting
on Dermal Fillers

Prepared for the Meeting of the
General and Plastic Surgery Devices
Advisory Panel

March 23, 2021

Table of Contents

List of Tables

List of Figures

List of Acronyms

AE	Adverse Event
ASPS	American Society of Plastic Surgeons
BDDE	1,4-butanediol diglycidyl ether
CaHA	Calcium Hydroxylapatite
ClinRO	Clinician Reported Outcome
CNS	Central Nervous System
CRF	Case Report Form
CTR	Common Treatment Site Response
FDA	Food and Drug Administration
FST	Fitzpatrick Skin Type
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic Acid
IDE	Investigational Device Exemption
ISR	Injection Site Reactions
MDR	Medical Device Report
OUS	Outside of the United States
PAS	Post-Approval Studies
PLLA	Poly-L-lactic Acid
PMA	Premarket Approval
PMMA	Polymethylmethacrylate
PRO	Patient Reported Outcome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SSED	Summary of Safety and Effectiveness Data
UDI	Unique Device Identifier
WSRS	Wrinkle Severity Rating Scale

Executive Summary

I. Purpose of Meeting

As required by section 513(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) for the purposes of discussing and making recommendations regarding the benefits and risks of dermal fillers concerning the following topics: (1) risks associated with intravascular injection of dermal fillers and (2) patient preference and informed decision-making.

II. Structure of the Meeting

The panel meeting will be held in a virtual format over the course of one day and includes time for open public comment, questions by the panel, and panel deliberation.

The morning session will focus on risks of dermal fillers, including intravascular injection-related adverse events and how best to assess and monitor patient safety. The afternoon session will focus on patient preference and the informed decision-making process.

III. Introduction

Dermal fillers, also known as injectable implants, soft tissue fillers, or wrinkle fillers, are medical device implants approved by the FDA for use in helping to create a fuller appearance in certain anatomic areas. These products have been on the market for over 30 years and have a variety of technological characteristics and indications for use.

Dermal filler injections have become one of the most commonly performed aesthetic procedures in the United States and abroad(1). Increased use has been accompanied by a concomitant increase in medical device reports (MDR) of adverse events, for both approved and unapproved fillers, techniques, and indications. Specifically, there are increasing reports of serious visual impairment, resulting from unintentional intravascular injection. Nearly every filler type has been associated with a severe complication leading to visual impairment, blindness, or stroke. FDA has responded with a multi-faceted set of premarket and postmarket actions. Premarket, the Agency has adopted a revised paradigm for clinical study design which includes safety assessments to characterize the risk of intravascular injection. In addition, all clinician and patient labeling includes warning and precaution statements informing the user of the risks associated with intravascular injection, including the symptoms associated with this event, and that intravascular injection can result in permanent and irreversible damage. Postmarket, the Agency actively and deliberately monitors annual reports and reviews adverse events in medical device reports (MDR) and literature. In May 2015, FDA released a Safety Communication in

response to reports of unintentional intravascular injection (2) and worked with manufacturers to retroactively revise approved labeling to incorporate appropriate warning statements.

Related to these efforts, FDA has recently taken steps to bring awareness to and address the alarming trend of injectable silicone being used for the unapproved purposes of gluteal or breast augmentation (3). When injected into vascular areas such as the buttocks, silicone can embolize and result in permanent damage to local tissues and can even lead to stroke or death.

Despite the efforts by the Agency to increase awareness of the risk of intravascular injection and the resulting serious adverse events through communications and revisions to labeling, we continue to receive anecdotal reports that prospective patients are not informed of this risk. As dermal fillers are aesthetic devices and an elective treatment, the patient makes the decision regarding the level of risk he or she is willing to accept in order to achieve the desired aesthetic outcome. Therefore, the purpose of this Panel meeting is to discuss potential actions that may be taken by the Agency both pre- and postmarket to ensure that the risks associated with intravascular injection are adequately communicated to patients and mitigated by healthcare providers, especially as new indications for use evolve and the use of dermal fillers continues to increase.

The FDA requests Panel input on several concrete steps the Agency proposes in order to address the risk of unintentional intravascular injection of dermal fillers.

While the first dermal fillers approved by the FDA in the 1980s were indicated for the correction of contour deficiencies (Zyderm PMA P800022), such as filling a wrinkle to mitigate the impact of aging, the modern landscape of dermal fillers has transformed considerably. Uses for dermal filler products now encompass indications specifically targeting augmentation and changes in contour, as well as gender-based and age-based cosmesis. Dermal fillers are being used increasingly in patients of diverse ethnic backgrounds, as well as in younger adult populations which were not previously represented in clinical studies. The shift in the uses for these devices has led to additional challenges as the assessment of benefit for facial augmentation may vary significantly with the expectations and demographics of the patient. These challenges are further highlighted by the changing demographics of the patients who are seeking treatment with dermal fillers. For example, in 2019 a greater percentage increase in individuals seeking aesthetic procedures was seen in Hispanic, African-American and Asian-American groups than in Caucasian groups (4). Additionally, although not necessarily reflective of the rates of non-invasive procedures, there has been a 15% increase in gender affirmation surgery between 2018 and 2019. The popularity of dermal fillers among an increasingly diverse population presents questions regarding how patient preference may be incorporated into effectiveness assessments, and whether the informed decision-making process may be improved.

The increasing popularity of dermal fillers across diverse populations for purely aesthetic indications poses dilemmas related to benefit versus risk assessment, and risk communication. During the meeting, the Panel will be asked to discuss ways in which patient perspective can be better integrated into the Agency's regulation of dermal filler products. In addition, FDA will seek Panel input on what additional steps FDA and other stakeholders can take to improve the informed decision-making process.

The FDA is committed to thoughtful, public dialogue concerning dermal filler safety and effectiveness and looks forward to a productive discussion.

IV. Device Description

Dermal fillers are soft, moldable products, either synthetic or sourced from bacteria or animals, that are injected into tissue with the intent to create a smoother or fuller appearance in, or adjacent to, the injected area. The dermal filler products discussed in this Executive Summary are Class III medical devices identified with product code LMH (implant, dermal, for aesthetic use) or PKY (implant, dermal, for aesthetic use in the hands). These products may be a medical device with a device constituent (e.g., collagen, poly-L-lactic acid, polymethylmethacrylate beads and/or cross-linked hyaluronic acid) or a combination product with a device constituent and an added drug constituent (e.g., lidocaine). Autologous dermal fillers such as fat or other tissues are outside the scope of this meeting.

Dermal filler products have received premarket approval (PMA) for: correction of nasolabial folds and facial acne scars on the cheeks of patients over the age of 21; lip augmentation; correction of age-related volume deficits in the midface in adults over the age of 21; augmentation of the chin region in subjects over the age of 21; volume loss in the dorsum of the hands; and restoration and/or correction of the signs of facial fat loss (lipoatrophy) in patients with HIV. Table 1 provides an overview of approved dermal fillers, organized by material properties and indications for use. Table 2 describes the types of filler materials and their associated considerations. Appendix I contains an expanded table of dermal filler products and their approved indications for use, current as of 01/29/2021. The tables highlight the increasing use of dermal fillers and their accelerating evolution and adoption. Prior to 2004, there were only 8 approved dermal filler PMAs (the first receiving approval in 1981, Zyderm). The period from 2005-2009 saw the approval of 9 additional PMAs. Six (6) PMAs were approved between 2010-2015, with an additional 16 PMAs receiving FDA approval from 2015 to the present.

Table 1. Approved Dermal Fillers Chart. Organized by Material Properties and Indications for Use, and Color Coded by Material Type[1]

	Naturally-derived						Synthetic		
	Absorbable								Non-absorbable
Indication	Collagen	HA – animal source	Hyaluronic Acid – bacterial source				Poly-L-lactic Acid	Calcium Hydroxyl-apatite	Poly-methyl-methacrylate
Chin			Restylane Defyne (P140029/S027)	Juvederm Voluma XC (P110033/S047)					
Cheek/ Midface			Restylane Lyft with Lidocaine (P040024/S073)	Juvederm Voluma XC (P110033)					
Lip			Restylane (P040024/S051) Restylane -L (P040024/S056) Restylane Silk (P040024/S072) Restylane Kysse (P140029/S021)	Juvederm Volbella XC (P110033/S018) Juvederm Ultra XC (P050047/S044)	Revanesse Lips+ (P160042/S010)				
Hands			Restylane Lyft with Lidocaine (P040024/S099)					Radiesse (P050052/S049)	
Perioral Lines			Restylane Kysse (P140029/S021) Restylane Silk (P040024/S072)	Juvederm Ultra XC (P050047/S044) Juvederm Volbella XC (P110033/S018)					
Nasolabial Folds	Zyderm (P800022) Zyplast (P800022/S011)		Restylane Silk (P040024/S072) Restylane-L (P040024/S039)	Juvederm 30 Juvederm 30HV Juvederm 24HV (P050047)	Revanesse Versa (P160042) Revanesse Versa+ (P160042/S003)	RHA 2, RHA 3, RHA 4 (P170002)	Sculptra Aesthetic (P030050/ S002)	Radiesse (P050052) Radiesse (+) (P050052/S052)	Artefill/Bellafill (P020012)
	CosmoDerm 1, CosmoDerm 2, CosmoPlast (P800022/S050)		Restylane (P040024) Restylane Defyne Restylane Refyne (P140029)	Juvederm Ultra XC Juvederm Ultra Plus XC (P050047/S005)	Captique (P030032/S002) Prevelle Silk (P030032/S007)	Perlane (P040024/ S006)			
	Evolence (P070013)	Hylaform (Hylan B) (P030032)	Restylane Lyft with Lidocaine (P040024/S073)	Juvederm Vollure XC (P110033/S020)	Belotero Balance (P090016) Belotero Balance (+) (P090016/S028)	Hydrelle/ Elevess (P050033)			
Acne Scars	Zyderm (P800022) Zyplast (P800022/S011) CosmoDerm 1, CosmoDerm 2, CosmoPlast (P800022/S050)								Artefill/Bellafill (P020012/S009)
HIV Lipoatrophy							Sculptra (P030050)	Radiesse (P050037)	
Scars	Fibrel (P850053)								

[1]For the full indication for use for each dermal filler listed above, please see Appendix I: Approved Dermal Filler Indications for Use.

Table 2 Description of Filler Material Types and Associated Considerations

Dermal Filler Material	Description/Unique Considerations
Collagen - Animal derived	• The first injectable devices approved by the FDA in 1981 utilized bovine collagen (Zyderm/Zyplast PMA P800022). These absorbable, xenogenic devices required skin testing before injection to evaluate for potential hypersensitivity reactions. Evolence (porcine-derived) did not require skin testing based on pre-market studies.
Collagen - Human derived	• CosmoDerm/CosmoPlast, FDA approved in 2003 (PMA P800022/S050), are absorbable, recombinant human collagen products produced and purified from cultured human neonatal foreskin cells. • Dermal fillers made of pure collagen (animal or human derived) have an approximate duration of 2-3 months (5).
Naturally derived Hyaluronic Acid	• Hyaluronic acid (HA), a polysaccharide naturally occurring in the extracellular matrix, generally derived from bacterial fermentation. HA is an absorbable material, and is often cross-linked with 1,4-butanediol diglycidyl ether (BDDE) to extend its duration. • The first FDA-approved HA filler was Restylane in 2003, (PMA P020023), and many additional HA fillers have been approved since then. Hylaform is an HA filler derived from rooster comb, FDA-approved in 2004 (PMA P030032). • Duration of effect varies depending on the material properties (e.g., degree of crosslinking, molecular weight of HA). The duration of effect reported in approved PMAs ranges from 6 months (6) up to 24 months (7).
Synthetic	• Poly-L-lactic Acid – Sculptra, an absorbable filler composed of polymer microspheres that are reconstituted in sterile water prior to injection. In a clinical study, the treatment results lasted for up to 2 years after the first treatment session, in most patients (8). • Calcium Hydroxylapatite – Radiesse, an absorbable filler consisting of 25-45 μm spherical particles suspended in a carboxymethylcellulose gel carrier. In a clinical study, the treatment effect lasted for 1 year after the first treatment session in all patients (9). • Polymethylmethacrylate – Bellafill, a non-absorbable filler containing 30-50 μm diameter microspheres of PMMA suspended in a gel containing 3.5% bovine collagen and 0.3% lidocaine hydrochloride. Requires skin testing before injection to evaluate for potential hypersensitivity reactions to bovine collagen. Treatment results are lasting. The microspheres are non-resorbable and therefore can only be surgically removed (10).

Pre-clinical Evaluation

All dermal filler products are evaluated for biocompatibility as implantable products in contact with tissue for longer than 30 days, according to the FDA guidance document, *"Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process' "*(11). If the product is collagen-based, the risk of hypersensitivity reaction is additionally assessed. Pre-clinical evaluation also includes assessment of product chemistry and materials engineering evaluation and testing.

Injection Techniques

Numerous injection methods have been described including linear threading, fanning, serial puncture, and bolus injections. The depth of injection depends on the specific filler indication and may range from the dermis to supraperiosteal planes. Although dermal fillers were initially approved for use with needles, cannula use has been approved for certain products and indications (see Appendix I). Often, injection technique and cannula versus needle use are up to the injector's personal preference and experience. The device labeling includes details regarding injection technique, plane of injection, maximum volume of injection, and safety precautions.

V. Risks Associated with Dermal Fillers

The risks of dermal fillers as observed in manufacturer-sponsored clinical studies and in the medical literature are provided in Table 3. Common risks of dermal fillers, which are frequently reported in clinical studies following injection are listed below. Less common risks are events which are less frequently reported in clinical studies or risks that have only been reported in the literature or through postmarket surveillance data. Filler use may be associated with uncommon but potentially serious adverse reactions like angioedema and anaphylaxis. Some of the most devastating risks of dermal filler injection result from intravascular injection, which may lead to irreversible damage.

Table 3. Risks of Dermal Fillers[1]

Common risks	Less common risks
• Swelling • Pain/tenderness • Firmness (induration) • Bruising • Redness • Discoloration • Itching	• Granuloma • Lumps/nodules • Injection site infection • Open or draining wounds • Allergic reaction • Unintended intravascular injection leading to: o Skin necrosis o Damage to underlying facial structures o Vision impairment/blindness and other eye or periocular complications o Stroke

[1] Please note that this table is not all-inclusive of all risks of dermal fillers. Risks are communicated in the labeling for each product.

Visual Impairment, Blindness, and Stroke

Visual impairment and blindness in the setting of aesthetic facial filler injection is thought to result from partial or complete interruption of blood flow to the central retinal artery. The prevailing mechanism proposed is inadvertent penetration of an artery in the face by the needle or cannula and subsequent intra-arterial injection of filler. Intra-arterial injection of filler under pressure into a branch of the ophthalmic artery that supplies blood to soft tissues of the face (e.g., supraorbital, dorsal nasal) may carry filler to the ophthalmic artery, interrupting blood flow to the retina, as depicted in **Figure 1**. Further embolization could result in filler reaching the internal carotid artery, resulting in occlusion of cerebral vasculature and stroke (12-15) .

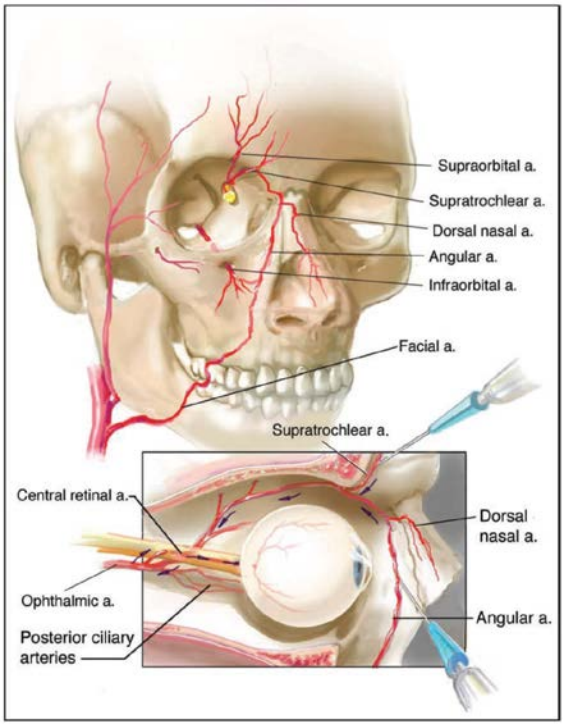

Figure 1. Vascular Anatomy of the Face. Inset demonstrates filler injected into the supratrochlear or the angular artery, which anastomoses with the supratrochlear artery. Filler can travel retrograde into the ophthalmic artery and its branches, obstructing blood supply to the retina. Beleznay K, Carruthers JDA, Humphrey S, Carruthers A, Jones D. Update on Avoiding and Treating Blindness From Fillers: A Recent Review of the World Literature. Aesthet Surg J. 2019;39(6):662-74 by permission of The American Society for Aesthetic Plastic Surgery (15).

Nearly every filler type has been associated with a severe complication leading to visual impairment, blindness, or stroke. Additionally, nearly every anatomic location on the face carries a risk for blindness (12, 14-16). Nevertheless, certain anatomic areas of the face may be more frequently associated with visual impairment and blindness. The glabella and nasal region are frequently reported sites of injection leading to visual complications, as are the forehead and nasolabial folds (14, 15, 17, 18). Injection in the temple, cheek, lip, chin, and eyelid have also all been associated with blindness (14, 15). Table 4 outlines the presentation of periocular embolism. It is noted that stroke is a commonly associated finding with periocular embolism leading to vision loss, as 18.8% of subjects with blindness were found to have central nervous system complications (15).

Table 4. Presentation of Periocular Embolism

	Sign and symptoms
Immediate, most common	Vision loss [a, b] Ocular pain [a, b]
May also be accompanied by	Ophthalmoplegia (weakness or paralysis of the eye muscles) [a,b, c] Ptosis (drooping of the eyelid)[a, b, c] Headache [a, b, c] Nausea [a, b, c] Vomiting [a, b, c] Soft tissue ischemia[c] Stroke[b,c]
[a] Carruthers 2014, [b] Beleznay 2015, [c] Beleznay 2019	

A variety of management strategies have been proposed for intravascular injection. For soft tissue necrosis, professional medical societies, such as the American Society for Dermatologic Surgery (ASDS), as well as expert panels (19, 20) have published guidelines of care for acute management. For blindness caused by intravascular filler, safe and reliable treatment has not been identified (15, 18). Rather, emphasis is on preparation and prevention of visual impairment secondary to filler injection, including identification of an ophthalmologist or retinal specialist in close proximity and access to a "filler crash kit" with the needed interventions (13). Prevention strategies include knowledge of injection site anatomy to avoid named vessels, and aspiration prior to injection. Injection guided by imaging such as ultrasound to visualize the vasculature has also been described.

VI. Medical Device Report (MDR) Analysis

Strengths and Limitations of MDR Data

The MDR system provides FDA with continuously updated information on medical device performance from patients, providers, and manufacturers. The FDA uses MDRs as part of its approach to monitor postmarket performance, detect potential safety issues, and contribute to benefit-risk assessments. MDRs are a valuable source of information; however, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data in the reports. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. As such, MDR numbers and data are evaluated in the context of the other available scientific information.

An all-time search of the MDR database for the dermal filler product codes LMH and PKY resulted in a total of 10,325 Serious Injury[2] reports as presented in **Figure 2**. The results show that the number of reports has steadily increased. The increases in 2014 and 2015 led to a Safety Communication from the Agency regarding the risks associated with intravascular injection (2). Since that time, the reports received by the Agency have continued to increase.

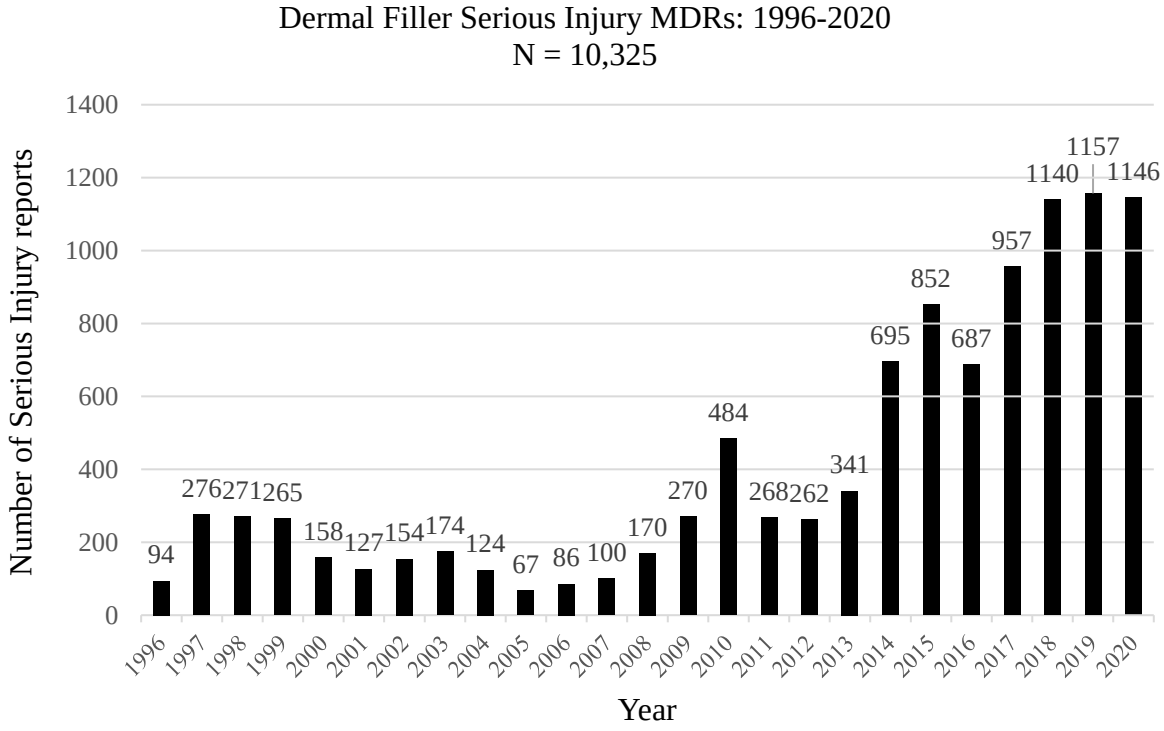

Figure 2. MDR Reports Received per Year. Serious Injury reports resulting from an all-time MDR search for the dermal filler product codes LMH and PKY. The results show that the number of reports has steadily increased.

A query of the MDR database for dermal filler product codes LMH and PKY from August 1, 2015 to August 1, 2020 identified 6,365 reports, 5009 of which were identified as Serious Injury reports as determined by the reporter. A breakdown of the top 10 problem codes for these 5009 Serious Injury reports is shown in **Figure 3**.

[2] The FDA defines serious injury as an injury or illness that is life threatening, results in permanent impairment of a body function or structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or structure.

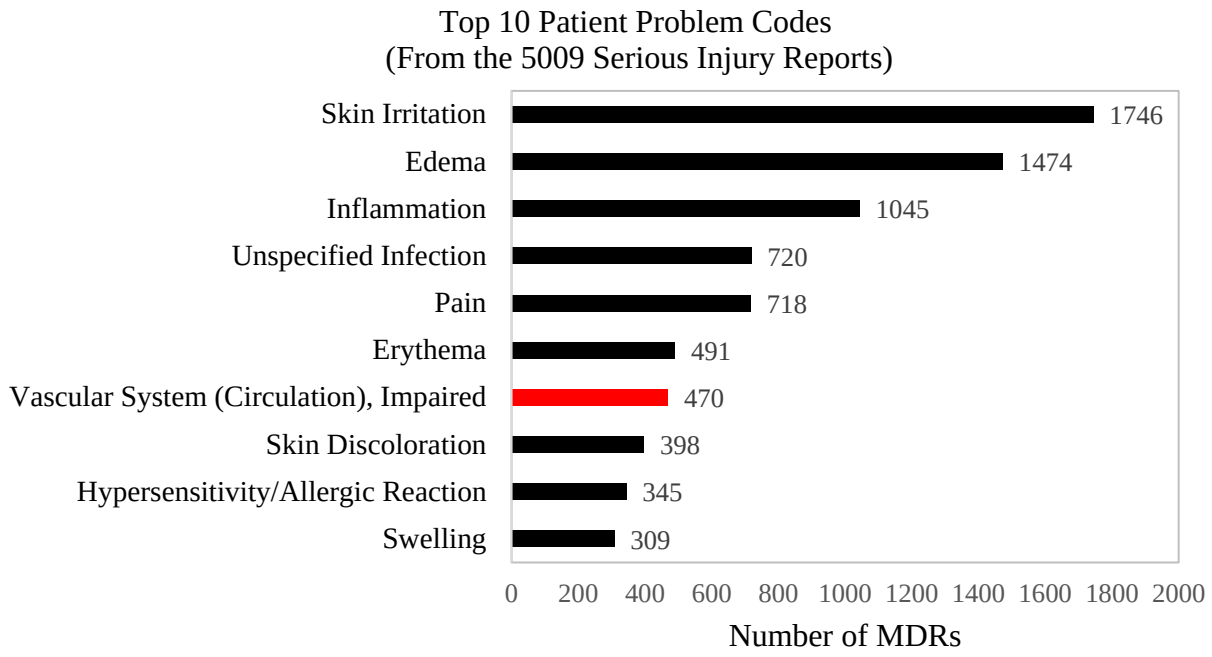

Figure 3. Top 10 Patient Problem Codes. The most commonly reported patient problem codes for the serious injury reports (N = 5009) received for product codes LMH and PKY from August 1, 2015 to August 1, 2020. The category "Vascular System (Circulation), Impaired" is highlighted in red (N = 470) for emphasis. The top reported codes include skin irritation (1746), edema (1474), and inflammation (1045). For some of the reports (391) there was no code available, and these were excluded from the Top 10 patient problem codes. Many of the reports (1263) stated that there was no known impact or consequence to the patient. Note that some reports listed multiple patient problem codes in a single MDR. This coding highlights some of the limitations of the MDR data.

MDRs Related to Vascular Events

Of the 5009 Serious Injury MDRs reported from August 1, 2015 to August 1, 2020, the most common serious adverse event was vascular system impairment. An analysis[3] of the Serious Injury MDRs for vascular system impairment resulted in 411 unique MDRs after duplicate reports were removed. **Figure 4** shows the breakdown of the areas of injection that reported vascular events. Note that MDR reports commonly list more than one injection area and include injection areas that are off-label. The majority of vascular events (374/411, 76.3%) reported local vascular impairment. Distant events were reported in 31/411 (7.5%) MDRs. The majority of the 411 MDRs reported skin discoloration (106/411, 26%), bruising (54/411, 13%) and pain (49/411, 12%).

[3] A search was conducted for the following search terms: Impaired Vascular System (Circulation), Necrosis, Ischemia, Occlusion, Embolism, Obstruction, Cerebrovascular Accident, Cerebral Infarction, Thrombosis, Embolus, Stenosis, Peripheral Vascular Disease, Chest Pain and Cardiopulmonary Arrest.

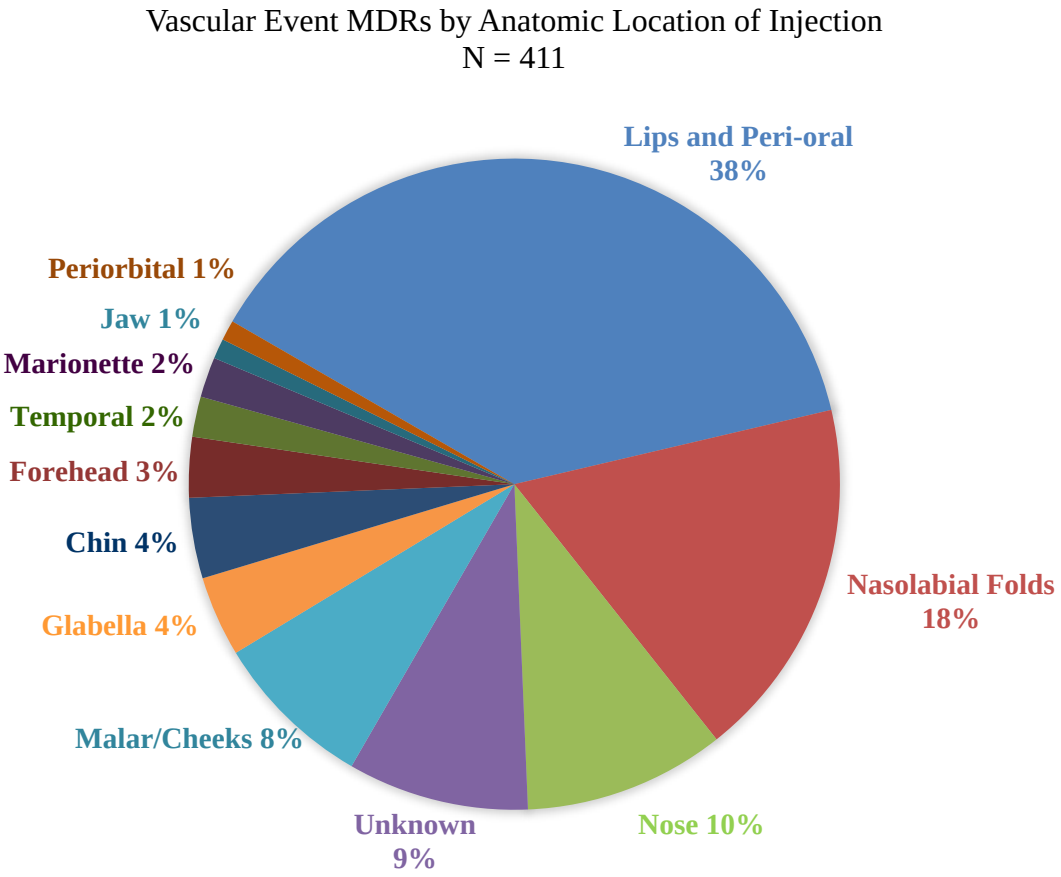

Figure 4. MDR Vascular Event Reports by Anatomic Location of Injection. The majority of vascular events occurred following injection into the lips and peri-oral area (157/411, 38%), nasolabial folds (75/411, 18%), and nose (39/411, 10%).

Vision-related MDRs

It is hypothesized that adverse events related to changes in vision or ophthalmic symptoms are the result of unintended injection into a blood vessel resulting in embolization. This is the most concerning risk associated with dermal fillers and can result in the most serious and often irreversible outcomes. A more detailed search[4] of the 5009 Serious Injury MDRs resulted in 92 MDRs reporting issues related to vision. Of these, 77 reported that the dermal filler was composed of Hyaluronic Acid (HA). Other reports identified dermal fillers that are composed of Polylactic Acid (PLLA) and Calcium Hydroxylapatite (CaHA).

Figure 5 demonstrates the frequency distribution of vision-related MDRs based on anatomic location of injection. A majority of the vision-related MDRs (50/123, 41%) reported that at least one of the injected areas was a region of the nose (Unknown Nose Area – 20, Nasal Dorsum - 19, Nasal Root - 4, Nasal Bridge – 4, and Nasal Tip - 3). The total number of events presented in

[4] A search was conducted for the following search terms: Optical Nerve Damage, Ptosis, Loss of Vison, Damage to Retina, Eye Injury, Blurred Vision, Impaired Vision, Visual Disturbances, Rise in Intraocular Pressure, Corneal Edema, Corneal Ulcer.

Figure 5 (N = 123) is greater than the number of vision-related MDRs (N = 92) as some reports described multiple areas of injection in a single MDR.

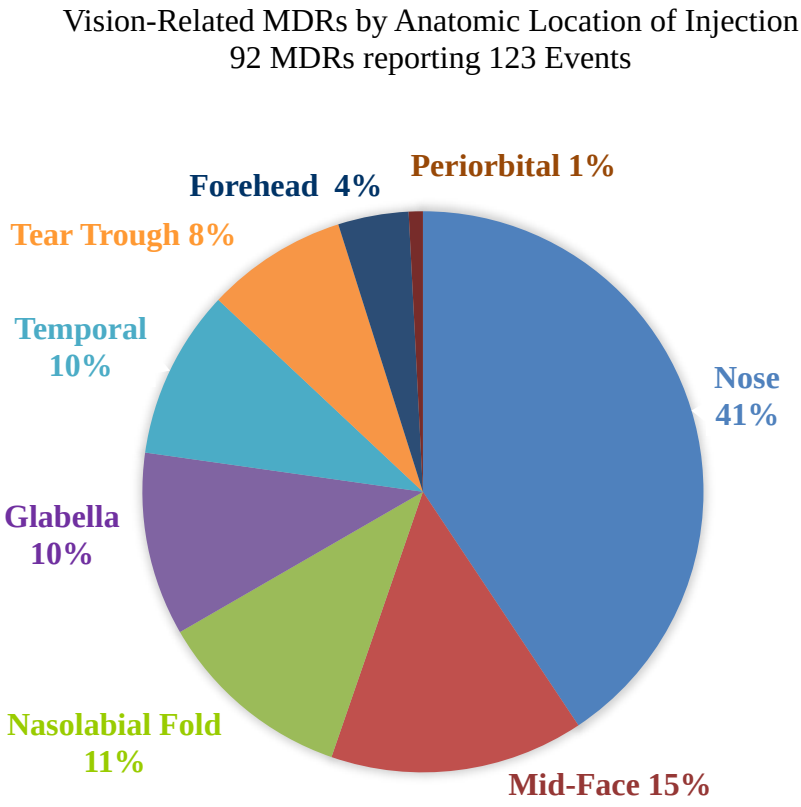

Figure 5. MDR Reports for Vision-Related Events by Anatomic Location of Injection. Please note that the total number of events presented here (n=123) is greater than the number of vision-related MDRs (92), as some reports described multiple areas of injection in a single MDR. The majority of the vision-related MDRs (50, 41%) reported that at least one of the injected areas was a region of the nose. The other notable injection areas include the mid-face (18, 15%), nasolabial fold (14, 11%), glabella (13, 10%), and temporal area (12, 10%).

Visual impairment developed immediately in 58% of patients (53/92) and developed 1-24 hours after injection in 20% of patients (18/92). Alarmingly, 9% of patients (8/92) developed vision loss more than 24 hours after injection.

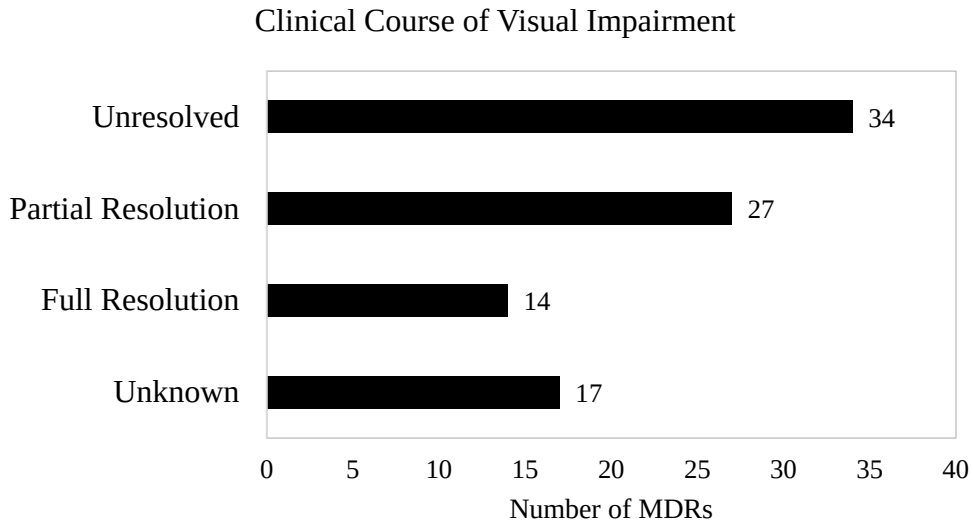

Figure 6. Clinical Course of Visual Impairment. Vision-related MDR reports (N = 92) were analyzed for clinical course of visual symptoms, categorized as Unresolved, Partial Resolution, Full Resolution, or Unknown.

Figure 6 shows the resolution of vision MDRs. At the time the MDR was reported, 37% had unresolved or permanent injuries, 29% had partial resolution and 15% had full resolution to baseline vision. The most commonly reported symptoms were: blurred vision, pain, partial or total blindness, headache, and dizziness. More favorable outcomes were reported in patients who received immediate treatment. Of the 92 vision-related MDRs, there were 17 reports (17/92, 19%) of patients who also experienced neurological symptoms. The most commonly reported symptoms were: drowsiness, non-reactive pupil, absent light reflex, facial drooping, and paralysis. Of note, this is closely aligned with the literature reports referenced above, which found that 18.8% of subjects with blindness from fillers also had central nervous system complications (15).

In summary, review of the MDR data from August 2015 to August 2020 with a particular focus on reports related to vascular events, especially visual impairment, identifies several anatomic areas of injection that may be considered higher risk for intravascular injection. **Figure 4** highlights the higher percentage of intravascular injection MDRs seen with the lips and peri-oral area, nasolabial folds, and nose. **Figure 5** underscores the higher percentage of visual impairment MDRs with injections performed in the nose. While MDR data cannot determine absolute risk or incidence, these areas align with what has been reported in literature, along with facial vascular anatomy (15).

VII. Clinical Study Considerations

Study Design

As noted above, there are reports of vascular impairment and vision-related symptoms in all areas of the face, including those on- and off-label. Due to the increasing reports of adverse events related to vision loss, and reports in the literature of new injection areas such as the areas around the eyes, nose, and glabella, FDA has incorporated additional measures into its regulatory strategy for dermal fillers. The following section discusses how clinical trials are designed to actively and deliberately monitor for visual impairment and to have measures in place to quickly treat subjects enrolled in the study if an incident of vascular compromise occurs.

Clinical trials that are intended to be conducted in the United States to support the approval of a dermal filler product or indication for use are reviewed and approved by FDA prior to study initiation through the investigational device exemption (IDE) process. Studies for dermal fillers vary in design, depending on the indications for use sought by the sponsor of the study. In addition, the study design may vary based on if the filler product has been previously approved for another indication, and if the product was previously studied in a controlled manner outside of the United States (OUS). Clinical study design should seek to incorporate patient preference information, as the evaluation of the benefits and risks of elective devices such as dermal fillers are considered to be preference sensitive. Patient preference information captures the value that patients place on aspects of a medical device. Patient preference information can impact how a clinical study is designed and be used to understand the impact of the clinical study results on patients. Therefore, it is important that the study design, which is discussed below, considers patient preference in the recruitment of study subjects. The material properties of the filler, such as cross-linking and anticipated duration of effect, affect study design as well. Common, notable components of these studies are described in Table 5. Please note that this list is not exhaustive.

Table 5 Elements of Dermal Filler Clinical Study Design

Study Objective	Defined to evaluate the clinical question of interest, for example: • Safety and preliminary effectiveness (feasibility study for a new dermal filler) • Safety and effectiveness (new indication for approved dermal filler • Non-inferiority study to approved comparator
Inclusion Criteria	• Typically involves baseline severity of the defect (e.g., wrinkle, volume loss) that is to be evaluated
Exclusion Criteria	• Patients receiving prior or concomitant aesthetic treatments in the proposed treatment area • Patients with certain underlying conditions (e.g., history of allergies) • Ophthalmic conditions that may confound the safety assessments for vision
Control (Options)	• No-treatment control • Sham-treatment control • Comparator (active control) device between-subjects or within-subjects in split-body design

Safety Evaluations	• Collection of injection site reactions or common treatment responses in a subject safety diary lasting 2-4 weeks • Adverse events throughout the study: incidence, severity, duration, relatedness, and resolution are recorded • Indication-specific assessments may also be included (e.g., hand functionality, speech, lip functionality, ability to smile broadly, cheek or lip sensation, etc.). • Monitoring for visual impairment as described in Table 6
Effectiveness Evaluations	• Clinician reported outcomes (ClinRO): Effectiveness scale typically developed and validated by the manufacturer • Reported as a responder rate: Percentage of subjects who showed a clinically meaningful response to treatment • Patient reported outcomes (PRO)
Repeat treatment	• Evaluates the safety and effectiveness of a second treatment, typically about 12 months after initial injection • Purpose is to reflect clinical practice, patients may seek re-treatment annually, and/or when the effect of the initial treatment has subsided • Subjects are monitored for safety as described and effectiveness may also be recorded

As discussed in detail in Section V. Risks Associated with Dermal Fillers, the most concerning risk associated with the use of dermal fillers is unintentional injection into a blood vessel. While the chances of this happening are low, if it does happen, the resulting complications can be serious and may be permanent, including vision abnormalities and blindness. Therefore, the following safety measures, shown in Table 6 and Table 7, have been identified by FDA as important and part of the Agency's efforts to actively and deliberately monitor for visual impairment to protect clinical trial participants.

Table 6. Safety Evaluations Specific to Vision Requested in Study Design

Inclusion/Exclusion Criteria	• Inclusion: Enrollment of subjects with normal vision assessments • Exclusion of subjects with abnormal vision assessments (poor visual acuity, abnormal confrontational visual field testing, etc.) • These criteria are provided because evaluation of vision following dermal filler injection may fail to identify subtle changes
Baseline assessments prior to injection	• Snellen visual acuity using a Snellen eye chart • Confrontational visual fields • Ocular motility
Post-injection assessments 30 minutes after treatment	• Snellen visual acuity using a Snellen eye chart • Confrontational visual fields • Ocular motility

Instructions to investigators	• In the event of intravascular injection, specific protocols (consistent with those recognized by national, professional societies) should be in place to ensure that intervention is safe and immediate • In the event of blindness or any ophthalmic signs or symptoms, subjects should undergo immediate evaluation by a retina specialist • Retina specialists near each of the study sites who are able to immediately examine subjects should be identified and informed of the study
Stopping rules	If there is a vascular embolic event leading to skin necrosis, vision loss, or stroke (may be amended to include additional risks if there are risks specific to the anatomic area intended to be injected): • The protocol should specify that enrollment and treatment at the investigational site is suspended • A root cause investigation should be conducted to determine the cause of the event and whether the outcome was anticipated or unanticipated • If the latter situation is observed, the entire study should be immediately suspended and no additional patients should be enrolled until the event can be properly characterized, and an appropriate mitigation strategy to avoid this unanticipated event can be devised
Enhanced reporting: Immediate reporting to the Agency of certain events	• Any incidence of visual disturbances (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes, etc.) • These reports should include the filler injected, injection site, depth of injection (e.g., subcutaneous or supraperiosteal), the injection volume, the symptoms that were observed, the time to onset, time to resolution, any interventions that were implemented, and clinical outcome, if known.

Table 7. Patient Communication Specific to Vision Requested in Study Design

Subject Safety Diary	Should include the following symptoms: • Changes in vision (i.e., loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes) • Skin changing color around the eyelids • Crusty or scabby skin around the eyelids • Pain • Headache • Dizziness

	• Confusion • Weakness or numbness in the arms or legs • Changes to consciousness or alertness • Difficulty speaking / speech impairment • Face droop
	Informs subjects of what to do in the case that they observe symptoms consistent with these adverse events (e.g., contact specialists such as the ophthalmologist, call 911 if experiencing signs of a stroke, etc.)
Informed Consent	• Describes risks of dermal fillers injection, including serious adverse events such as vascular occlusion and vision loss, which may be permanent • Describes procedures in case of adverse event, such as further medical or surgical management

Additional Safety Measures

Premarket Clinical Evaluation
As noted above, the study design can vary based on the body of available information, proposed indication for use, and dermal filler properties. In addition, there are increasing reports in the literature of new injection areas such as the areas around the eyes, nose, and glabella. Based on the information available in the Agency's MDR database, these areas may be of heightened concern regarding the risks associated with vascular occlusion leading to vision-related adverse events. The following additional safety measures in Table 8 have been identified by FDA to mitigate and/or characterize the risk associated with unintentional injection into a blood vessel:

Table 8. Additional Safety Measures

Training Requirement	FDA can require that treatment with the investigational device in a clinical study be performed by qualified individuals by reason of their scientific training and/or experience per 21 CFR 812.36
Additional Testing	Additional or alternative vision tests, such as: • fundoscopic examinations • automated perimetry • retinal photography +/- fluorescein angiography • alternative visual acuity charts
Interval Examination	Delayed contralateral treatment to permit visual safety assessments and/or a retinal specialist exam between injections
Imaging Guidance	Use of ultrasound or other imaging to visualize the location of injection

Neurological Assessment	Evaluation by a neurologist +/- neurologic imaging for subjects with vision-related complications, including blindness

Given that the incidence of vision loss is low and the typical enrollment goals of dermal filler studies include 100-300 subjects, a case of vision loss is not expected to be seen during the course of a premarket clinical study. Therefore, it is unsurprising that since the initiation of vision assessments in dermal filler clinical studies, a severe adverse event related to vision loss secondary to intravascular injection has not been reported in studies supporting approved PMAs. The assessments in Table 6 have been requested in premarket clinical studies for all indications; anatomic areas with more frequent reports of vascular occlusion-related events, however, may potentially require additional vision safety measures (Table 8), although these have not been routinely requested by FDA. These assessments are not a part of routine clinical practice for dermal filler injections and are not currently included in the labeling as part of the directions for use. FDA is interested in implementing an approach, through device labeling, for incorporating early detection of vascular occlusion into clinical practice, which would provide the appropriate level of safety monitoring for the patient while being feasible for clinicians. It is also important to note that while there are more reports of visual disturbances, vascular occlusion may also result in neurologic effects such as stroke which are less commonly reported. As stated previously, 18.8% of patients with blindness were found to have central nervous system complications (15). Therefore, additional neurological assessments may be warranted for any patient who experiences a vision-related complication.

Postmarket Clinical Evaluation

In a premarket clinical study, the investigators receive training from the manufacturer for the procedure in question and agree to be a part of the clinical study. However, while dermal fillers are labeled for prescription use only, in postmarket clinical use the injector may not have adequate training to safely inject the device for a particular indication, especially in the areas with more frequent reports of vascular occlusion-related events. Therefore, device-specific and indication-specific training of licensed practitioners is one measure that may mitigate the risks associated with unintentional injection into a blood vessel after premarket approval. Consensus recommendations published in literature note that well-trained and experienced providers can mitigate risk of complications. Additionally, knowledge of the anatomy is identified as a method to mitigate risk. However, it is not clear that there is published evidence demonstrating that training does decrease the risk of vascular occlusion-related events. In one randomized, controlled trial, injection technique was correlated with AE rate (not intravascular events specifically) but training was not assessed (21). There appears to be a paucity of evidence quantifying the effectiveness of training, or identifying the types of training that may be most appropriate to mitigate risk of adverse events such as unintentional intravascular injection.(21).

As noted above, the size of premarket clinical studies is small (100-300 subjects). While this sample size is sufficient to evaluate the effectiveness of treatment and to characterize common injection site responses and local adverse events (Table 3), it may not adequately characterize less common events such as intravascular occlusion or embolism. Therefore, postmarket clinical studies may help characterize the risk associated with events such as visual and neurologic impairment. A registry—either narrowly focused on patients who have experienced visual

impairment or broader in scope, encompassing dermal filler patients—may be an alternative approach.

Effectiveness Evaluation

As indications have shifted from the filling of a wrinkle to the augmentation and alteration of facial contour, these indications may be difficult to assess using the traditional methods of clinician-reported outcomes. Consequently, dermal filler study designs have adapted to increasingly incorporate input from the patient and to be more patient-centered. As new indications emerge, such as increasing reports in the literature of nose augmentation and augmentation of areas of the body such as the décolletage and buttocks, it is important for the Agency to continue to update and improve review practices to adequately assess the benefits and risks of device use and disseminate this information to the end user, who is making an elective decision regarding whether treatment is right for them.

Effectiveness evaluation in dermal filler clinical studies includes a combination of clinician- and patient-reported outcomes. As these are aesthetic devices and elective procedures, FDA considers the incorporation of the patient perspective critical to the study of the benefits associated with dermal fillers. The prospective patient plays a central role in determining what aesthetic treatment is right for them, especially when there are many alternatives. Therefore, FDA considers the comparison of treatments with regards to safety and effectiveness to be an important piece of the informed decision-making process. However, the current implementation of clinician-reported effectiveness outcomes may not provide optimal information for the patient to fully evaluate device benefits, as illustrated in Table 9.

Table 9. Primary Effectiveness Evaluation

Primary Effectiveness Evaluation: Clinician Reported Outcome (ClinRO)	
Description	• Sponsor-specific scale • Assesses wrinkle and/or defect severity • Typically a 4 - 6 grade photonumeric scale • Validated to demonstrate good intra- and inter-rater agreement • Validated to demonstrate the ability of a change on the scale to represent a clinically meaningful change • Scale may be validated using photographs or through live evaluation
Example that has been used in dermal filler clinical studies	Wrinkle Severity Rating Scale, WSRS (22) (used as primary endpoint in six PMAs to support an indication for use for the nasolabial fold) • Validated to evaluate the severity of the nasolabial fold • 5-point photonumeric scale (1-5 grade rating) ranging from a grade of 1 (absent) no visible nasolabial fold to a grade of 5 (extreme) extremely deep and long nasolabial fold, detrimental to facial appearance • The subject is assessed by the blinded evaluator at baseline (either through live or photographic evaluation), and again at timepoints

	throughout the study to determine if the subject is a responder to treatment • A subject is considered a responder if the subject has demonstrated a clinically meaningful improvement in the scale or outcome of interest • On the WSRS, an improvement that is greater than or equal to one grade is a responder
Challenges	• The results of clinical studies for the same indication often cannot be compared • The effectiveness scale is often proprietary, as it is developed and validated by the sponsor of the clinical study • A review of effectiveness scales used to evaluate the nasolabial folds showed that out of 13 different PMAs, 7 different effectiveness scales were used, based on a combination of live and photographic evaluation, with primary effectiveness endpoint evaluations performed at various timepoints ranging from 12 weeks to 13 months after treatment • Proprietary scales are not publicly available for other interested study sponsors seeking similar indications • Proprietary scales vary between manufacturers for the same indication • Clinician-reported outcomes may not align with patient preference
Possible Solutions	• The use of publicly available validated effectiveness scales (e.g., from literature, previously conducted clinical studies) that are clinically meaningful for the indication for use • Promotion of more publicly available validated clinical outcome assessment tools by encouraging medical device development tools (MDDT) in this arena (23). This would publicize the validity of the outcome measure to encourage use across study sponsors

Patient-Reported Outcomes

Patient perspectives refer to information relating to patients' experiences with a disease or condition or its management. This may be useful for identifying outcomes that are most important to patients, and understanding benefit-risk tradeoffs for treatment. The patient's perspective is particularly important in evaluating the success of aesthetic treatments because the patient is the ultimate consumer of the medical product and can provide additional assurance that the endpoint is clinically meaningful. Dermal filler clinical studies typically include input from the patient as secondary or ancillary effectiveness endpoints. The assessments include validated patient-reported outcomes (PROs) assessed by subjects throughout the study. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else (24).

As noted above in Table 9, the primary effectiveness evaluation is traditionally a ClinRO and does not incorporate input from the patient. In addition, the use of PROs faces similar challenges to those outlined in Table 9. While there are some widely used PROs, including FACE-Q and the global aesthetic improvement scale (GAIS), the latter is not a validated PRO and study sponsors often include their own proprietary measures of subject satisfaction, which may not be adequately validated or widely available for use.

As new indications for use emerge, including augmentation and facial contouring, the definition of a clinically meaningful outcome increasingly depends on patient preferences and expectations. In addition, it's important that the use of ClinROs be supplemented by PROs that are validated for the proposed indication for use. The Agency continues to consider the use of validated ClinROs important as an objective assessment of device effectiveness. Therefore, the Agency proposes that ClinROs and PROs be evaluated as co-primary effectiveness endpoints. It's important that these two measures be validated for the indication for use, and publicly available for use such that the end user can directly compare the performance between different dermal filler products.

One solution to the challenges outlined above is provided by FDA's voluntary program for qualification of medical device development tools (MDDT) for use in evaluating devices (23). An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making. Examples of MDDTs are clinical outcome assessments, assessments of biomarkers, and non-clinical assessment methods or models. Clinical study sponsors are encouraged to use the MDDT program to qualify ClinROs and PROs that can be used to evaluate the effectiveness of dermal fillers.

A second solution would be to eliminate the use of ClinROs or revise the structure of clinical studies such that a PRO is the primary endpoint and a ClinRO is a secondary endpoint. This would reduce the challenges outlined in Table 9 with regards to multiple proprietary ClinROs being used. However, there is value in an objective measurement tool that is intended to be assessed by the healthcare provider. In addition, a similar challenge may emerge with PROs, as study sponsors develop their proprietary PROs to use for primary endpoint evaluation.

Patient Perspective

While PRO measures provide a snapshot of a patient's own assessment of an outcome at a given point in time, they do not convey how much the patient values one specified outcome when compared to other potential outcomes. Instead, this is encompassed by patient preference information (PPI). PPI is useful in evaluating a device's benefit-risk profile when patient decisions are "preference sensitive," as in the case of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. Because dermal fillers are elective devices in which the patient is the end user, patient perspective on benefit and tolerance for risk should be incorporated into effectiveness evaluations, including both ClinRO and PRO measures. The definition of clinical success may vary depending on patient demographics and the perspectives of different patient populations. As an example, for a facial contouring indication, each patient has specific aesthetic goals and a certain tolerance level for

risk of intravascular injection to achieve these goals. This level of risk that is acceptable may differ by the patient demographic, such as age, ethnicity, or gender identity. Additionally, differing indications for treatment are also tied to patient perspective: a patient seeking correction of age-related changes in the lips may have different ideas of clinical success compared to a patient seeking lip augmentation. Current effectiveness measures may not adequately incorporate these diverse perspectives. To address this issue, FDA proposes that the design and validation of ClinROs and PROs should represent diverse patient populations based on gender (including transgender and nonbinary patients), age, and ethnicity, as well as a diversity of aesthetic treatment goals for each patient group.

The safety and effectiveness outcomes of a clinical study may also vary based on patient demographics. Dermal filler clinical studies typically define the age[5] of the intended study population, the gender distribution, as well as the distribution by Fitzpatrick Skin Type (FST). It is important to include a diversity of skin types in the study, so that the study population is reflective of the demographics of the United States (25). In recent years, the Agency has encouraged studies to include enrollment goals by FST, with at least 20% of subjects from FST IV – VI and 10% from FST V – VI. However, these enrollment goals may not be reflective of the distribution of FSTs within the U.S. population. In addition, enrollment goals that better align with the demographics of the broader patient population may be appropriate for other key subgroups such as age, gender, or ethnicity. There may also be indications where the demographics of the patient populations who are seeking specific treatments differ from that of the general US population, as well as indications where the patient demographics evolve over time (e.g., increasing representation of men). To address this issue, we propose that enrollment goals should be set to ensure that the study population reflects the intended patient population, whether that is the US population as a whole or a subgroup that is demonstrated to be representative of the patients seeking a particular treatment. Similarly, study documentation and design should additionally seek to be inclusive of diverse patients (e.g., Case Report Forms with non-binary gender options).

VIII. Informed Decision-Making

To make an informed decision about a medical device, it's important that a patient have an understanding of the effects and expectations associated with that device. Especially in the setting of aesthetic or elective procedures such as dermal filler injections, it is important to discuss both the possible risks and the anticipated benefits to ensure that patients are making treatment choices based on clear expectations. As dermal filler studies and indications gradually evolve to include new intended uses and anatomical areas, it is important to convey these risks to patients. As discussed above, more and more indications are focused on augmentation and contour deficiencies instead of traditional wrinkle filling. In addition, anatomic areas with more reports of vascular occlusion-related events, such as the nose, may be associated with greater risk.

[5] The FDA considers individuals 21 years of age and younger to be part of the pediatric population, up to but not including the 22nd birthday (FDA Guidance Pediatric Medical Devices).

Despite the steps that FDA has taken to ensure that the risks of dermal fillers are present in labeling and that clinical study participants are informed and monitored, FDA believes that patients will benefit from more structured and standardized presentation of dermal filler risks and benefits.

Dermal Filler Patient Labeling

Dermal fillers are approved with both clinician and patient labeling. Clinician labeling includes indications, directions for use, contraindications, warnings, precautions, adverse events, and a summary of the clinical studies that supported approval. Patient labeling is designed to assist in the informed decision-making process by patients. Elements of patient labeling are shown in Table 10.

Table 10. Elements of Patient Labeling

Device Description	• Materials and composition • Description of packaging
Indications for Use	• Description of the defect or anatomic area addressed by injection • Specific patient population (e.g., age)
Precautions and Contraindications	• Periprocedural exposures (e.g., anesthetic) • Populations or anatomical regions where safety or effectiveness has not been established • Health conditions or concurrent therapies that should be communicated to the provider
Risks	• Possible pain or discomfort • Common side effects and their severity and duration • Risks of other adverse events • Precautions regarding visual or neurologic symptoms • Serious adverse events, even if they are not common • Risk that certain adverse events will require further treatment, such as antibiotics, injection, or surgical procedure
Benefits	• Expected effectiveness • Duration of effectiveness
Alternatives	• Other approved dermal fillers for the same indication for use • Other aesthetic treatments that may achieve a similar aesthetic outcome • Alternative anesthetic choices
Other Information	• How the clinical study was performed • Adverse events and effectiveness results seen in the clinical study • Postmarket surveillance and information about the MedWatch adverse event reporting program

FDA continuously monitors reports of injuries caused by dermal fillers. Labeling of an approved PMA is updated when new safety information is found in MDRs and literature. FDA can, and often does, request that manufacturers make revisions of the labeling to reflect new information. In May 2015, FDA published a safety communication alerting providers and consumers about the possibility of serious injuries that may occur due to unintentional injection of dermal filler into blood vessels in the face (2).This safety communication was motivated both by FDA MDR post-market surveillance data and an increasing number of reports in peer-reviewed literature describing filler-associated vascular occlusion .

After publishing the safety communication, FDA worked with manufacturers who market dermal filler implants to update their labeling to include information on events associated with intravascular injection of dermal filler material in the face including vision impairment, blindness, stroke, skin necrosis, and damage to underlying facial structures. Since then, FDA has ensured that this information is present in all new approved labeling and that new safety information is presented in labeling.

While FDA ensures that the aforementioned information is present in patient labeling, there may be ways to improve the way in which this information is communicated. Potential communication strategies are described in Table 11.

Table 11. Strategies to Communicate Labeling Information

Patient Labeling	• Standardized patient labeling with consistent presentation of benefits and risks • Structure and content to be based on Table 10 above • Inclusion of additional information on the increased risks associated with higher-risk injection areas
Boxed Warning	• Boxed warning regarding the risk of intravascular injection
Patient Decision Checklist	• Content to include information and risks of dermal filler injections listed in Table 10 • Specific mention of the risks of soft tissue necrosis, blindness and stroke • If approved through the PMA process, areas with more reports of vascular occlusion-related events should require an additional informed decision-making checklist acknowledging the acceptance of increased risk • Allows for patients and providers to affirmatively acknowledge that each item was read and discussed

Post-Procedure Monitoring

While providers are responsible for communicating labeling information to patients for the purposes of informed decision-making, there are no mechanisms to ensure that patients receive the appropriate post-procedure information. Post-procedure information would have the following benefits:

1. Record of the device that was used for injection and its unique device identifier (UDI)(26)
2. Information about common treatment responses, along with serious adverse events
3. Allow for continuity of care should a patient transition care between providers
4. Allow for a patient to follow device updates, such as for safety or potential recall
5. Instructions for medical device reporting and manufacturer contact information

While labeling information is often available on manufacturer websites, patients may not necessarily be aware of the type of filler they have received. Additionally, generic information on manufacturer websites does not provide unique device identification (UDI) information regarding the specific device that was used. FDA would like to propose to the Panel a method by which the appropriate information can be conveyed to patients.

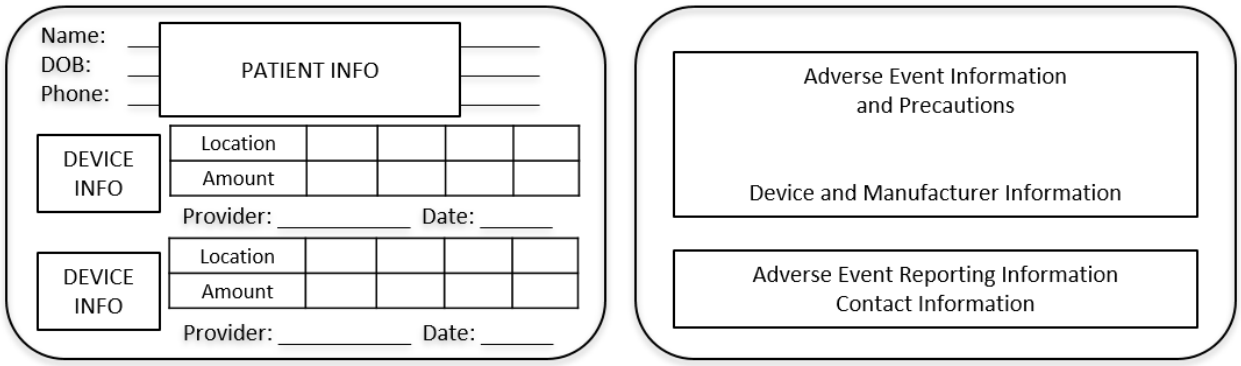

Figure 7. Example Mock-Up of a Portable Patient Device Card

An example would be the concept of a patient device card, which can either be a physical or digital card as shown in **Figure 7**. This card would contain information regarding the specific device that was used, along with post-procedure instructions, especially regarding adverse events. The card may contain information regarding communicating adverse events directly to the Sponsor and information about medical device reporting to FDA, thereby better capturing events that occur with these devices. Additionally, these cards may allow for patients to stay up-to-date as new information is learned about device safety.

IX. Appendix I: Approved Dermal Filler Indications for Use

Table 12. FDA Approved Fillers.

Trade Name	Material	Applicant	PMA Number	Decision Date	Approved For
RESTYLANE DEFYNE	Sodium Hyaluronate with Lidocaine	Q-Med AB	P140029/ S027	1/29/2021	Indicated for injection into the mid-to deep dermis (subcutaneous and/or supraperiosteal) for augmentation of the chin region to improve the chin profile in patients with mild to moderate chin retrusion over the age of 21.
REVANESSE LIPS+	Hyaluronic Acid, Lidocaine	Prollenium Medical Technologies Inc.	P160042/ S010	9/29/2020	Indicated for submucosal implantation for lip augmentation in patients 22 years of age or older
JUVÉDERM® VOLUMA™ XC	Hyaluronic Acid	Allergan	P110033/ S047	6/12/2020	JUVÉDERM® VOLUMA™ XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for augmentation of the chin region to improve the chin profile in adults over the age of 21
RESTYLANE KYSSE	Hyaluronic Acid with Lidocaine	Q-Med AB	P140029/ S021	3/26/2020	Injection into the lips for lip augmentation and for correction of upper perioral rhytids in patients over the age of 21
JUVÉDERM® VOLUMA™ XC	Hyaluronic Acid	Allergan	P110033/ S042	8/29/2016	Approval for an update to the labeling for Juvederm Voluma XC to include the use of cannula. Indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21.
BELOTERO BALANCE (+) LIDOCAINE	Hyaluronic Acid	Merz Pharmaceuticals	P090016/ S028	8/29/2019	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds such as nasolabial folds.
RESTYLANE LYFT WITH LIDOCAINE	Hyaluronic Acid with Lidocaine	Q-Med AB	P040024/ S101	11/2/2018	Indicated for use of a small bore, blunt tip cannula with Restylane Lyft with Lidocaine for cheek augmentation and

					the correction of age related midface contour deficiencies in patients over the age of 21
REVANESSE VERSA +	Hyaluronic Acid, Lidocaine	Prollenium Medical Technologies Inc.	P160042/ S003	8/2/2018	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, in adults 22 years of age or more
RESTYLANE LYFT WITH LIDOCAINE	Hyaluronic Acid, Lidocaine	Q-Med AB	P040024/ S099	5/18/2018	Injectable gel indicated for injection into the subcutaneous plane in the dorsal hand to correct volume deficit in patients over the age of 21.
REVANESSE VERSA	Hyaluronic Acid, Lidocaine	Prollenium Medical Technologies Inc.	P160042/ S001	10/2/2017	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, in adults 22 years of age or more
REVANESSE ULTRA	Hyaluronic Acid	Prollenium Medical Technologies Inc.	P160042	8/4/2017	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, in adults 22 years of age or more
RHA 2	Hyaluronic Acid, Lidocaine	Teoxane S.A.	P170002	10/19/2017	Injectable gel indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds, in adults aged 22 years or older
RHA 3	Hyaluronic Acid, Lidocaine	Teoxane S.A.	P170002	10/19/2017	Injectable gel indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds, in adults aged 22 years or older
RHA 4	Hyaluronic Acid, Lidocaine	Teoxane S.A.	P170002	10/19/2017	Injectable gel indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds, in adults aged 22 years or older

RESTYLANE SILK	Hyaluronic Acid with Lidocaine	Q-Med AB	P040024/ S096	10/11/2017	Approval for use of a small bore, blunt tip cannula with Restylane Silk for submucosal implantation for lip augmentation in patients over the age of 21
JUVEDERM VOLLURE XC	Hyaluronic Acid	Allergan	P110033/ S020	3/17/2017	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in adults over the age of 21.
RESTYLANE REFYNE, RESTYLANE DEFYNE	Sodium Hyaluronate with Lidocaine	Q-Med AB	P140029	12/9/2016	Restylane Refyne is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial fold) in patients over the age of 21. Restylane Defyne is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe deep facial wrinkles and folds (such as nasolabial fold) in patients over the age of 21.
JUVEDERM VOLBELLA XC	Hyaluronic Acid with Lidocaine	Allergan	P110033/ S018	5/31/2016	Injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21.
JUVEDERM ULTRA XC	Hyaluronic Acid with Lidocaine	Allergan	P050047/ S044	9/30/2015	Indicated for injection into the lips and perioral area for lip augmentation in adults over the age of 21
RESTYLANE LYFT WITH LIDOCAINE	Hylauronic acid with lidocaine	Galderma Laboratories	P040024/ S073	7/1/2015	Indicated for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21
RADIESSE	Hydroxyl-apatite	Bioform Medical, Inc.	P050052/ S049	6/4/2015	Subdermal implantation for hand augmentation to correct volume loss in the dorsum of the hands.
RADIESSE (+) LIDOCAINE	Hydroxyl-apatite	Merz Pharmaceuticals	P050052/ S052	1/30/2015	Addition of the lidocaine to Radiesse, indicated for subdermal implantation for correction of moderate to severe facial wrinkles and folds, including nasolabial folds

BELLAFILL	Polymethylmethacrylate Beads, Collagen and Lidocaine.	Suneva Medical, Inc.	P020012/S009	12/23/2014	Indicated for the correction of nasolabial folds and moderate to severe, atrophic, distensible facial acne scars on the cheek in patients over the age of 21 years
RESTYLANE SILK	Hyaluronic Acid with Lidocaine	Valeant Pharmaceuticals North America LLC/Medicis	P040024/S072	6/13/2014	Indicated for lip augmentation and dermal implantation for correction of perioral rhytids (wrinkles around the lips) in patients over the age of 21.
JUVEDERM VOLUMA XC	Hyaluronic Acid with Lidocaine	Allergan	P110033	10/22/2013	Deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21.
RESTYLANE-L INJECTABLE GEL	Hyaluronic Acid with Lidocaine	Medicis Aesthetics Holdings, Inc.	P040024/S056	8/30/2012	Indicated for submucosal implantation for lip augmentation in patients over the age of 21.
BELOTERO BALANCE	Hyaluronic Acid	Merz Pharmaceuticals	P090016	11/14/2011	Injection into facial tissue to smooth wrinkles and folds, especially around the nose and mouth (nasolabial folds).
RESTYLANE INJECTABLE GEL	Hyaluronic Acid	Medicis Aesthetics Holdings, Inc	P040024/S051	10/11/2011	Lip augmentation in those over the age of 21 years.
RESTYLANE L AND PERLANE L INJECTABLE GELS	Hyaluronic Acid with Lidocaine	Q-med AB	P040024/S039	1/29/2010	The addition of 0.3% lidocaine into Restylane and Perlane
JUVEDERM ULTRA XC JUVEDERM ULTRA PLUS XC	Hyaluronic Acid with Lidocaine	Allergan	P050047/S005	1/7/2010	The addition of 0.3% Lidocaine into Juvederm Ultra and Juvederm Ultra Plus. Indicated for use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
SCULPTRA AESTHETIC	Poly-L-Lactic Acid (PLLA)	Sanofi Aventis U.S.	P030050/S002	7/28/2009	Use in shallow to deep nasolabial fold contour deficiencies and other facial wrinkles.
EVOLENCE COLLAGEN FILLER	Porcine Collagen	Colbar Lifescience l	P070013	6/27/2008	The correction of moderate to deep facial wrinkles and folds (such as nasolabial folds).

PREVELLE SILK	Hyaluronic Acid with Lidocaine	Genzyme Biosurgery	P030032/ S007	2/26/2008	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
PERLANE INJECTABLE GEL	Hyaluronic Acid	Medicis Aesthetics Holdings, Inc	P040024/ S006	5/2/2007	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.
RADIESSE 1.3CC AND 0.3CC	Hydroxyl-apatite	Bioform Medical, Inc	P050037	12/22/2006	Restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV.
RADIESSE INJECTABLE IMPLANT	Hydroxyl-apatite	Bioform Medical, Inc	P050052	12/22/2006	Subdermal implantation for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
HYDRELLE/ ELEVESS	Hyaluronic Acid with Lidocaine	Anika Therapeutics	P050033	12/20/2006	Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
ARTEFILL	Polymethylmethacrylate Beads, Collagen and Lidocaine.	Suneva Medical, Inc.	P020012	10/27/2006	Use in facial tissue around the mouth (i.e., nasolabial folds).
JUVEDERM 24HV, JUVEDERM 30, JUVEDERM 30HV	Hyaluronic Acid	Allergan	P050047	6/2/2006	Use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
RESTYLANE INJECTABLE GEL	Hyaluronic Acid	Medicis Aesthetics Holdings, Inc	P040024	3/25/2005	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
CAPTIQUE INJECTABLE GEL	Hyaluronic Acid	Genzyme Biosurgery	P030032/ S002	11/12/2004	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
SCULPTRA	Poly-L-Lactic Acid (PLLA)	Sanofi Aventis U.S.	P030050	8/3/2004	Restoration and/or correction of the signs of facial fat loss (facial lipoatrophy) in people with Human

					Immunodeficiency Virus (HIV).
HYLAFORM (HYLAN B GEL)	Modified hyaluronic acid derived from a bird (avian) source	Genzyme Biosurgery	P030032	4/22/2004	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
RESTYLANE INJECTABLE GEL	Hyaluronic Acid	Q-med Ab	P020023	12/12/2003	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
COSMODERM 1 COSMODERM 2 COSMOPLAST	Human Collagen	Inamed Corporation	P800022/ S050	3/11/2003	Injection into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.
FIBREL	Collagen	Serono Laboratories	P850053	2/26/1988	The correction of depressed cutaneous scars which are distendable by manual stretching of the scar borders.
ZYPLAST	Bovine Collagen	Collagen Corp.	P800022/ S011	6/24/1985	Use in mid to deep dermal tissues for correction of contour deficiencies.
ZYDERM COLLAGEN IMPLANT	Bovine Collagen	Allergan	P800022	9/18/1981	Use in the dermis for correction of contour deficiencies of this soft tissue.

*Please note that this table may not be inclusive of all FDA approved fillers or filler indications. Updated as of 1/29/2021.

X. References

1. ASPS. American Society of Plastic Surgeons: Plastic Surgery Statistics Report 2019 [8/13/2020]. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-full-report-2019.pdf.
2. FDA. Labeling Change Request for Soft Tissue Fillers 2015 [12/8/2020]. Available from: https://www.fda.gov/media/92608/download.
3. FDA. FDA Warns Against Use of Injectable Silicone for Body Contouring and Enhancement: FDA Safety Communication 2017 [02/23/2021]. Available from: https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-injectable-silicone-body-contouring-and-enhancement-fda-safety-communication.
4. ASPS. American Society of Plastic Surgery Plastic Surgery Statistics Report 2019 [08/13/2020]. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-full-report-2019.pdf.
5. AAD. American Academy of Dermatology Fillers: FAQs [02/05/2021]. Available from: https://www.aad.org/public/cosmetic/wrinkles/fillers-faqs.
6. FDA. Boletero Balance P090016 Summary of Safety and Effectiveness Data (SSED) 2011. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf9/P090016b.pdf.
7. FDA. Juvederm Voluma XC P110033 Summary of Safety and Effectiveness Data (SSED) 2013. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110033b.pdf.
8. FDA. Sculptra Patient Labeling 2004 [12/04/2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030050D.pdf.
9. FDA. Radiesse Labeling 2006 [12/04/2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050037C.pdf.
10. FDA. Artefill Labeling 2006 [12/04/2020]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf2/P020012C.pdf.
11. FDA. Guidance on Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" 2016 [01/14/2021]. Available from: https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/Use-of-International-Standard-ISO-109931-Biological-evaluation-of-medical-devices.pdf.
12. Carruthers JDA, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. Plast Reconstr Surg. 2014;134(6):1197-201. Epub 2014/11/22. doi: 10.1097/PRS.0000000000000754. PubMed PMID: 25415089.
13. DeLorenzi C. Complications of injectable fillers, part 2: vascular complications. Aesthet Surg J. 2014;34(4):584-600. Epub 2014/04/03. doi: 10.1177/1090820X14525035. PubMed PMID: 24692598.
14. Beleznay K, Carruthers JD, Humphrey S, Jones D. Avoiding and Treating Blindness From Fillers: A Review of the World Literature. Dermatol Surg. 2015;41(10):1097-117. Epub 2015/09/12. doi: 10.1097/DSS.0000000000000486. PubMed PMID: 26356847.

15. Beleznay K, Carruthers JDA, Humphrey S, Carruthers A, Jones D. Update on Avoiding and Treating Blindness From Fillers: A Recent Review of the World Literature. Aesthet Surg J. 2019;39(6):662-74. Epub 2019/02/26. doi: 10.1093/asj/sjz053. PubMed PMID: 30805636.
16. Rayess HM, Svider PF, Hanba C, Patel VS, DeJoseph LM, Carron M, et al. A Cross-sectional Analysis of Adverse Events and Litigation for Injectable Fillers. JAMA Facial Plast Surg. 2018;20(3):207-14. Epub 2017/12/23. doi: 10.1001/jamafacial.2017.1888. PubMed PMID: 29270603; PubMed Central PMCID: PMCPMC6145786.
17. Park SW, Woo SJ, Park KH, Huh JW, Jung C, Kwon OK. Iatrogenic retinal artery occlusion caused by cosmetic facial filler injections. Am J Ophthalmol. 2012;154(4):653-62 e1. Epub 2012/07/28. doi: 10.1016/j.ajo.2012.04.019. PubMed PMID: 22835509.
18. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. Blindness following cosmetic injections of the face. Plast Reconstr Surg. 2012;129(4):995-1012. Epub 2012/03/30. doi: 10.1097/PRS.0b013e3182442363. PubMed PMID: 22456369.
19. Urdiales-Galvez F, Delgado NE, Figueiredo V, Lajo-Plaza JV, Mira M, Moreno A, et al. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. Aesthetic Plast Surg. 2018;42(2):498-510. Epub 2018/01/07. doi: 10.1007/s00266-017-1063-0. PubMed PMID: 29305643; PubMed Central PMCID: PMCPMC5840246.
20. Alam M, Gladstone H, Kramer EM, Murphy JP, Jr., Nouri K, Neuhaus IM, et al. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008;34 Suppl 1:S115-48. Epub 2008/07/02. doi: 10.1111/j.1524-4725.2008.34253.x. PubMed PMID: 18547175.
21. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. Dermatol Surg. 2008;34 Suppl 1:S105-9. Epub 2008/07/02. doi: 10.1111/j.1524-4725.2008.34251.x. PubMed PMID: 18547173.
22. Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5(1):49-52. Epub 2004/02/26. doi: 10.2165/00128071-200405010-00007. PubMed PMID: 14979743.
23. FDA. Guidance on Qualification of Medical Device Development Tools (MDDT) 2017 [01/14/2021]. Available from: https://www.fda.gov/media/87134/download.
24. FDA. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009 [02/23/2021]. Available from: https://www.fda.gov/media/77832/download.
25. FDA. Collection of Race and Ethnicity Data in Clinical Trials: Guidance for Industry and Food and Drug Administration Staff 2016 [01/19/2021]. Available from: https://www.fda.gov/media/75453/download.
26. FDA. Guidance on Unique Device Identification: Direct Marking of Devices 2017 [1/14/2021]. Available from: https://www.fda.gov/media/92100/download.