FDA Executive Summary
General Issues Panel
Meeting on Dermal Fillers

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

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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 a new indication for use for dermal filler devices in the décolletage area and making recommendations regarding risks associated with new indications for use such as in the décolletage area, the potential impact of filler material on imaging studies and clinical exams (e.g., breast cancer screening), premarket and post-market study assessments for benefit and risk, removal of dermal filler implant material, and patient preference.

II. Structure of 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.

III. Introduction

Dermal fillers are injectable devices which are used to fill wrinkles and provide volume. Devices have been approved for various indications that include different anatomical areas on the face and the hands in adults over the age of 21. Note that FDA approves dermal fillers for specific, defined anatomic locations because different anatomic sub-regions (e.g., nasolabial folds, lips, chin, jawline, cheeks/midface, infraorbital hollows) present risks specific to the underlying anatomy (e.g., nerves, blood vessels, muscles, and organs) and the function of that anatomic region. Approved devices also have a variety of technological characteristics, and some have been on the market for over 30 years. Dermal fillers are prescription use devices for use by licensed practitioners and for certain indications, manufacturers may only distribute the device to providers that implement the device-specific use training program. In 2024, dermal filler procedures experienced continued growth, maintaining their position as the second most popular minimally invasive cosmetic treatment in the United States. An estimated 6,264,287 total dermal filler procedures were performed, encompassing both hyaluronic acid-based fillers and non-hyaluronic acid formulations [1].

With the growth of dermal filler usage, new indications for use (i.e., use of a specific filler in a specific defined anatomic location) are being proposed and new variations of devices are being designed. There has been increased interest in new injection locations for dermal fillers, such as in the décolletage area (also referred to as the décolleté), the thighs, and areas of the body other than the face. Several clinical studies have been completed for dermal filler devices in various indications. Additionally, post-market data are available that have identified common risks, such as injection site reactions, and less common risks, such as delayed nodule formation or unintended intravascular injection. It is expected that novel, un-studied injection locations would also carry these known risks, but there may be additional risks unique to the different anatomical locations or the different technological characteristics of the devices that would be injected in the new locations.

One new area of interest is the use of dermal fillers for correction of wrinkles in the décolletage area. Use in this area brings additional risks such as potential interference with imaging and screening methods for cancer, as the skin of the décolletage area is included in the anatomic region of the breast. It is possible

that false negative or false positive cancer diagnoses could be observed if the presence of filler material interferes with common imaging techniques used to detect breast cancer. For example, calcium hydroxylapatite (CaHA) microspheres of RADIESSE® injectable implant are visible on CT scans as well as in standard, plain radiography (x-rays). A post-approval study was conducted to evaluate the impact of the injectable implant on visualization of the bones under X-ray and the results of the study showed that there was "obscuring" on radiographic imaging. Similarly, Macrolane, a hyaluronic acid-based dermal filler, was previously used for breast augmentation outside the United States, but it was withdrawn from use in this indication because the presence of the device made diagnosis of breast cancer more difficult. The device was reported to obscure the breast tissue on mammography and it was also detectable in ultrasound and MRI examination of the breasts [2, 3]. However, the impact of different materials on imaging in the décolletage area has not been specifically studied. There is also potential for device migration or adverse events associated with filler injection, such as nodule or lump formation, leading to false positive cancer diagnoses and unnecessary interventions (biopsies, etc.) or false negative cancer diagnoses. Other possible risks include potential to affect the vascular and/or lymphatic systems in the area and potential to impact breast feeding. **The panel will be asked for input on proposed strategies to assess these risks associated with injection of dermal fillers near the breast.**

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 consist of material components (e.g., collagen, poly-L-lactic acid (PLLA), polymethylmethacrylate beads, calcium hydroxylapatite, and/or cross-linked hyaluronic acid) or may be combination products with an added drug constituent (e.g., lidocaine or mepivacaine). Autologous dermal fillers such as fat or other tissues are outside the scope of this meeting.

Since the 2021 General Issues Panel Meeting on Dermal Fillers held on March 23, 2021, till May 28, 2025, there have been 13 dermal filler PMAs approved for new products or new indications. These dermal fillers contain bacterial-source crosslinked hyaluronic acid, PLLA, or calcium hydroxylapatite. In addition to the lip, cheek, perioral rhytids and nasolabial folds, three new indications received approval, including infraorbital hollowing, jawline, and temple augmentation. For pain control, one PMA was approved for a product including mepivacaine.

Dermal filler products have received premarket approval (PMA) for the following indications[a]:

- Correction of nasolabial folds and facial acne scars on the cheeks of patients over the age of 21
- Lip augmentation over the age of 21
- Correction of perioral rhytids in patients over the age of 21
- 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
- Restoration and/or correction of the signs of facial fat loss (lipoatrophy) in patients with HIV
- Augment the temple region in adults over the age of 21

[a] See Appendix for a complete list of dermal filler devices that have received premarket approval and the approved indications for use.

- Improvement of infraorbital hollowing in adults over the age of 21
- Improvement of jawline definition in adults over the age of 21

The Appendix lists all dermal fillers including indications for use and material type, organized by approval date.

Risks Associated with Dermal Fillers

As with any medical procedure, there are risks involved with the use of dermal fillers. Most side effects associated with dermal fillers, such as swelling and bruising, occur shortly after injection and typically resolve in a few days to weeks. In some cases, side effects may emerge weeks, months, or years later.

The risks of dermal fillers as observed in manufacturer-sponsored clinical studies and in the medical literature are provided in Table 1. 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 post-market 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 including vision loss.

It is important to note that subpopulations of patients may be at higher risks for some potential adverse events. For example, dermal filler procedures can lead to post-inflammatory hyperpigmentation, particularly in patients with FST IV-VI [4]. Granulomatous Mastitis is a rare inflammatory condition with unclear etiology that may be more likely in Hispanic patients [5]. This condition has not yet been observed in relation to dermal filler use but should be considered when studying dermal fillers for use in new indications near the breast.

Dermal fillers are also being used increasingly in younger adult populations - in 2024, it is estimated that thousands of minimally invasive cosmetic procedures involving HA and non-HA fillers were performed on patients 19 and younger [1] – although these younger patients are less frequently represented in clinical studies. In premarket studies conducted for FDA approvals since February of 2021, the average age of patients ranged from 44 to 61. Furthermore, long-term impact of repeated use by subjects was not evaluated. While clinical trials typically include touch-up treatment and retreatment of subjects, risks related to longer, repeated use in subjects and potential for cumulative effects have not been established. It is not clear how repeated uses may change the benefit or risk profiles of these devices.

Table 11. Risks of Dermal Fillers[1]

Common risks	Less common risks
• Swelling • Pain/tenderness • Firmness (induration) • Bruising • Redness	• Granuloma • Lumps/nodules • Injection site infection • Open or draining wounds • Allergic reaction • Necrosis (tissue death)

• Discoloration • Itching • Rash • Difficulty in performing activities (only observed when injected into the back of the hand)	• Unintended intravascular injection leading to: o Skin necrosis o Damage to underlying structures o Vision impairment/blindness and other eye or periocular complications o Stroke • Reports of bone resorption after supraperiosteal injection

[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.

The most serious risk associated with dermal fillers is accidental injection into a blood vessel. Filler that enters a blood vessel can cause skin necrosis, stroke, or blindness. While the chances of this happening are low, if it does happen, the resulting complications can be serious and may be permanent.

Injection-related visual compromise (IRVC) 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. Further embolization could result in filler reaching the internal carotid artery, resulting in occlusion of cerebral vasculature and stroke [6-10]. Nearly every filler type has been associated with a severe complication leading to visual impairment, blindness, or stroke.

Based on preliminary review of published literature and Medical Device Reports (MDRs), the FDA has identified three cases from MDRs and as many as 60 cases in seven publications of bone resorption in the chin, jaw, midface, or forehead in patients who received supraperiosteal (directly on the bone) hyaluronic acid dermal filler injections [11-17]. In all cases, patients did not have symptoms, and the findings of bone resorption have been identified on imaging including CT or dental x-ray that was conducted for various other medical reasons such as dental, chin, or jaw procedures. In addition, the reports of bone resorption have been limited to use of hyaluronic acid dermal fillers and not dermal fillers made of other materials.

V. Décolletage indications

As cited above, the use of dermal fillers for aesthetic purposes continues to increase in the U.S. Along with an increase in overall usage, there continue to be new anatomic regions that have been identified and treated with these devices. The use of dermal filler devices to treat the décolletage region has been investigated and reported for a number of years. A product has recently received regulatory approval for injection into this anatomic region outside of the U.S., though to-date, there are no dermal filler devices approved by the Agency for the treatment of the décolletage [18-23].

Specific risks with this indication

As discussed at the March 23, 2021, General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting, dermal filler injections are associated with serious adverse events, including skin necrosis, blindness, and stroke. As described above, these adverse events result from intravascular injection, leading to occlusion of the affected vasculature. With regards to the décolletage region, given the proximity of the décolletage to breast tissue, there are unique risks and concerns associated with treatment of this anatomic location in addition to the risk of intravascular injection which is inherent to treatment with dermal filler anywhere in the body. Potential risks associated with dermal filler injection in the décolletage region include breast cancer misdiagnosis, interference with diagnostic imaging, intravascular and lymphatic complications, and filler migration.

Breast cancer is the second leading cause of cancer death in women, and the lifetime risk of a woman in the US developing breast cancer is approximately 13% [24]. Due to this risk, screening mammograms scheduled on a regular basis are recommended for all women at average risk. Because study participants for clinical studies involving dermal filler devices, including dermal fillers investigated for the treatment of the décolletage, have been predominantly female, there are new questions regarding the safety of these treatments and the potential impact of dermal filler injection into the décolletage on breast cancer screening [25]. More specifically, there are concerns that injection into the décolletage may result in 1) positive findings during clinical breast examinations, where palpable filler nodules or granulomas are mistaken for suspicious breast masses, or conversely, interference where the presence of filler material masks or obscures detection of breast pathology, 2) interference during imaging for breast cancer screening, and 3) complications of breast feeding and/or the local lymphatic system.

Dermal fillers have been known to cause granulomas, lumps/bumps, and/or nodules, which can occur weeks to years after injection with the device. Migration of dermal filler following injection has also long been described. The presence of a mass in or near breast tissue due to prior dermal filler injection may lead to a positive diagnosis for a breast mass during routine clinical examinations. This may then result in additional testing, such as imaging and/or a biopsy. Furthermore, in patients with a history of dermal filler injection in the décolletage region, healthcare practitioners may incorrectly attribute a newly identified mass to a delayed complication from the previous dermal filler procedure, such as granulomatous inflammation, nodule formation, or filler migration. This may result in a potentially malignant lesion being dismissed as a benign filler-related complication. Subsequently, this can lead to critical delays in appropriate oncological evaluation, tissue sampling, and initiation of treatment, potentially compromising patient outcomes and prognosis.

In addition, dermal filler materials in the décolletage region raise significant concern due to their potential to negatively impact breast cancer screening imaging studies. Screening for breast cancer most commonly involves mammography, though MRI and ultrasound are also used to evaluate the breast tissues. The effect on these imaging studies from different dermal fillers of various chemical compositions into the décolletage is unclear. Further highlighting this risk is the concern in the literature regarding the potential for dermal fillers to mask an underlying malignancy [26]. In addition, cervical lymph node enlargement due to complications from facial dermal fillers injected years prior has been reported, and if similar findings occur following injection into the décolletage, this may further confound screening efforts for breast cancer [27]. Misdiagnosis via these screening tests may result in additional unnecessary testing and/or procedures as well as delayed diagnosis of these patients.

Finally, with the proximity of the décolletage region to the breasts, there is concern that injection into the décolletage has the potential to impact breast feeding and the lymphatic drainage system of the breast. However, there is limited information related to this potential risk in the literature, and additional input from an advisory panel is needed.

The panel will be asked about additional risks to be considered and specific subpopulations to be studied or excluded for this new indication for use.

Medical Device Reporting (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 post-market performance, detect potential safety issues, and contribute to benefit-risk assessments. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, duplicate, 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 a result, the actual number of adverse events is expected to be substantially higher than what is reported through the MDR system. This discrepancy is likely even more pronounced for unapproved devices, where users may be less inclined to report issues or may not be aware of the reporting mechanisms. As such, MDR numbers and data are evaluated in the context of the other available scientific information and ongoing post-market surveillance efforts. In general, FDA does not have access to complete clinical details in adverse event reporting and must rely on descriptions provided.

An all-time search of the MDR database for the dermal filler product codes LMH and PKY resulted in a total of 17,768 Serious Injury reports, as categorized by the reporter. The search results show that the number of reports has steadily increased. The increases in 2014 (n=786) and 2015 (n=887) led to a Safety Communication from the Agency regarding the risks associated with intravascular injection [28]. Since that time, the reports received by the Agency have continued to increase, resulting in 1,478 reports received in 2023 and 1,179 reports received in 2024 (up to November 2024).

Vascular system impairment continues to be a common serious adverse event as reported in the 2021 Dermal Filler Panel. Other common serious adverse events reported include abscess (n=1,235), nodules (n=1,038), obstruction/occlusion (n=986), and granulomas (n=846). Of note, 3 Serious Injury MDRs reported a newly recognized adverse event, bone resorption after supraperiosteal injection.

MDRs Related to Décolletage Indications

Even though injection into the décolletage is not an approved indication for dermal filler devices in the United States, several MDR reports have been received for this off-label indication. An analysis of the Serious Injury MDRs for unapproved upper body anatomic locations, including the neck, décolletage/chest, and breast, resulted in 186 unique MDRs after duplicate reports were removed. **Figure 1** shows the Serious Injury reports received from an all-time MDR search. Note that these new, unapproved indications started to be reported in 2007. The number of reports, associated with unapproved upper body anatomic indications, including neck, chest/décolletage/décolleté, and breast, show an increasing trend since 2019.

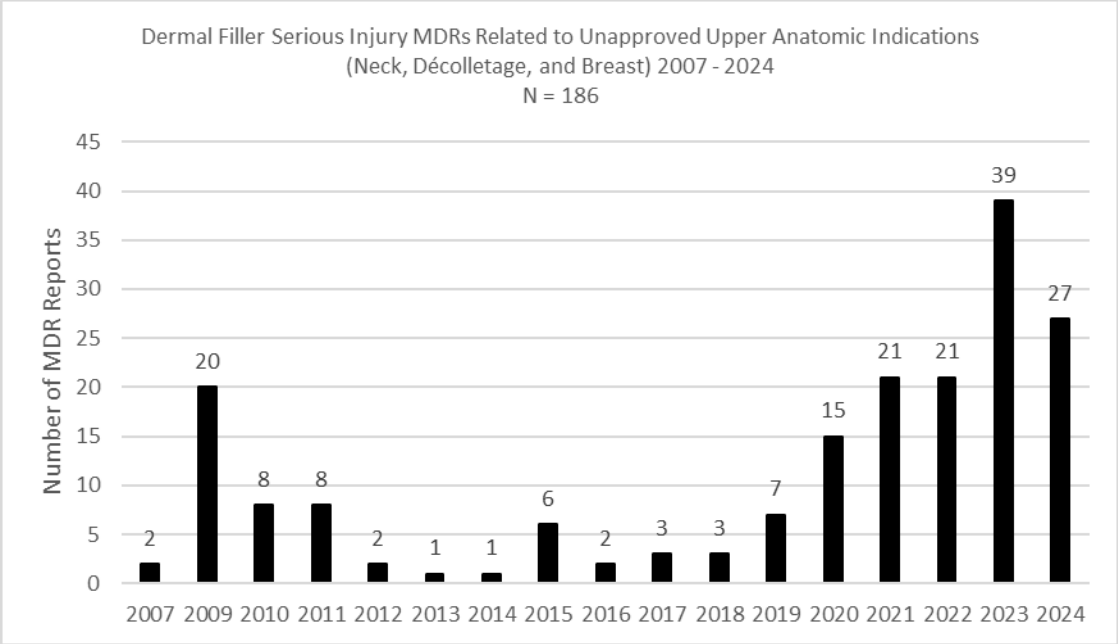

Figure 1 MDR Reports Received per Year (content current as of 11/08/2024).

Figures 2 and 3 show the breakdown of the unapproved upper body anatomic areas of injection by anatomic location and dermal filler composition, respectively. Note that the majority of serious injury reports were reported for the neck area with 162/186 (87.1%); while the décolletage/décolleté/chest area reported 20/186 (10.8%) serious injury events, and the MDR reports for the breast area listed 6/186 (3.2%). Regarding the dermal filler composition, the most commonly listed dermal filler type in the unapproved upper body anatomic indications is HA dermal fillers in 77/186 (41.4%), followed by CaHA dermal fillers with 52/186 (30%), and PLLA dermal filler with 49/186 (26.3%) MDRs. For additional context, the 2024 Plastic Surgery Statistics Report published by the American Society of Plastic Surgeons reports that 5,331,426 procedures were performed using HA fillers in 2023 compared to 932,861 procedures performed using non-HA fillers [1].

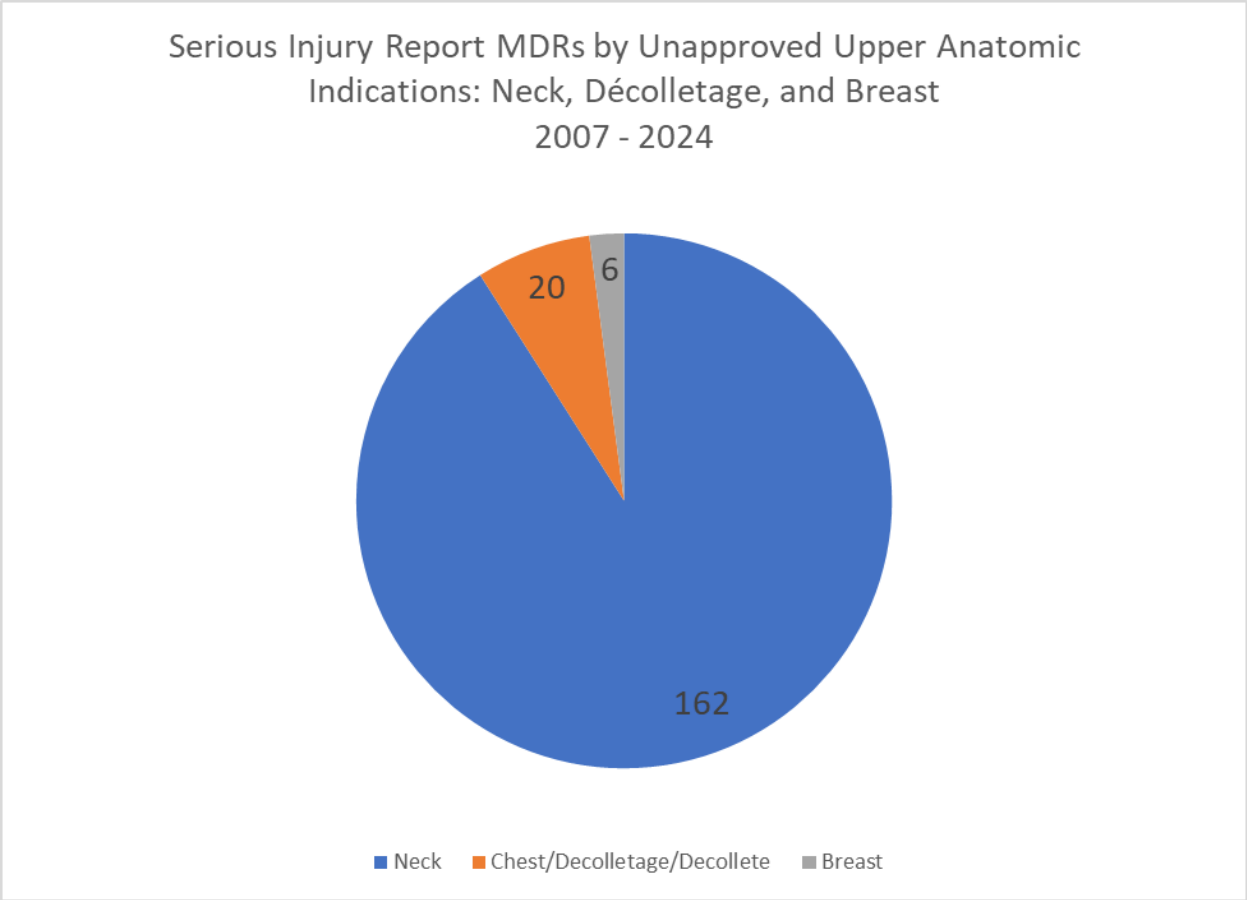

Figure 2. MDR Reports Received by Unapproved Upper Anatomic Areas: Neck, Décolletage, and Breast. Note that some reports listed multiple indications in a single MDR.

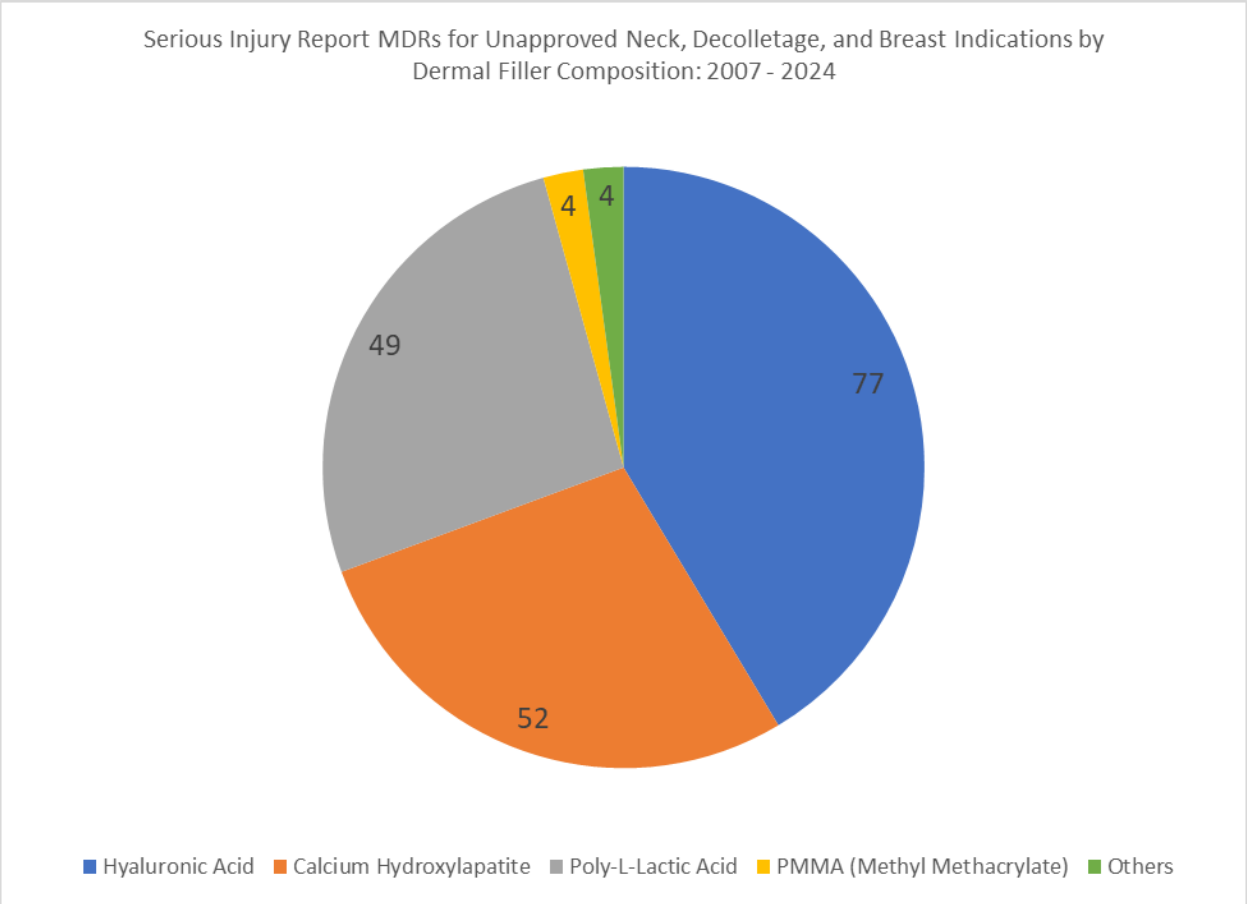

Figure 3. MDR Reports Received by Dermal Filler Composition in Unapproved Upper Anatomical Locations, including Neck, Décolletage, and Breast.

A breakdown of the top 25 problem codes for these 186 Serious Injury reports is shown in **Figure 4**. Nodule formation is the most common serious adverse event (n=38). Other common serious adverse events include granulomas and swollen lymph nodes/glands. These serious adverse events are of particular interest when determining safety of new dermal filler indications, such as the décolletage area, and the potential impact of the aesthetic treatment on breast cancer screening.

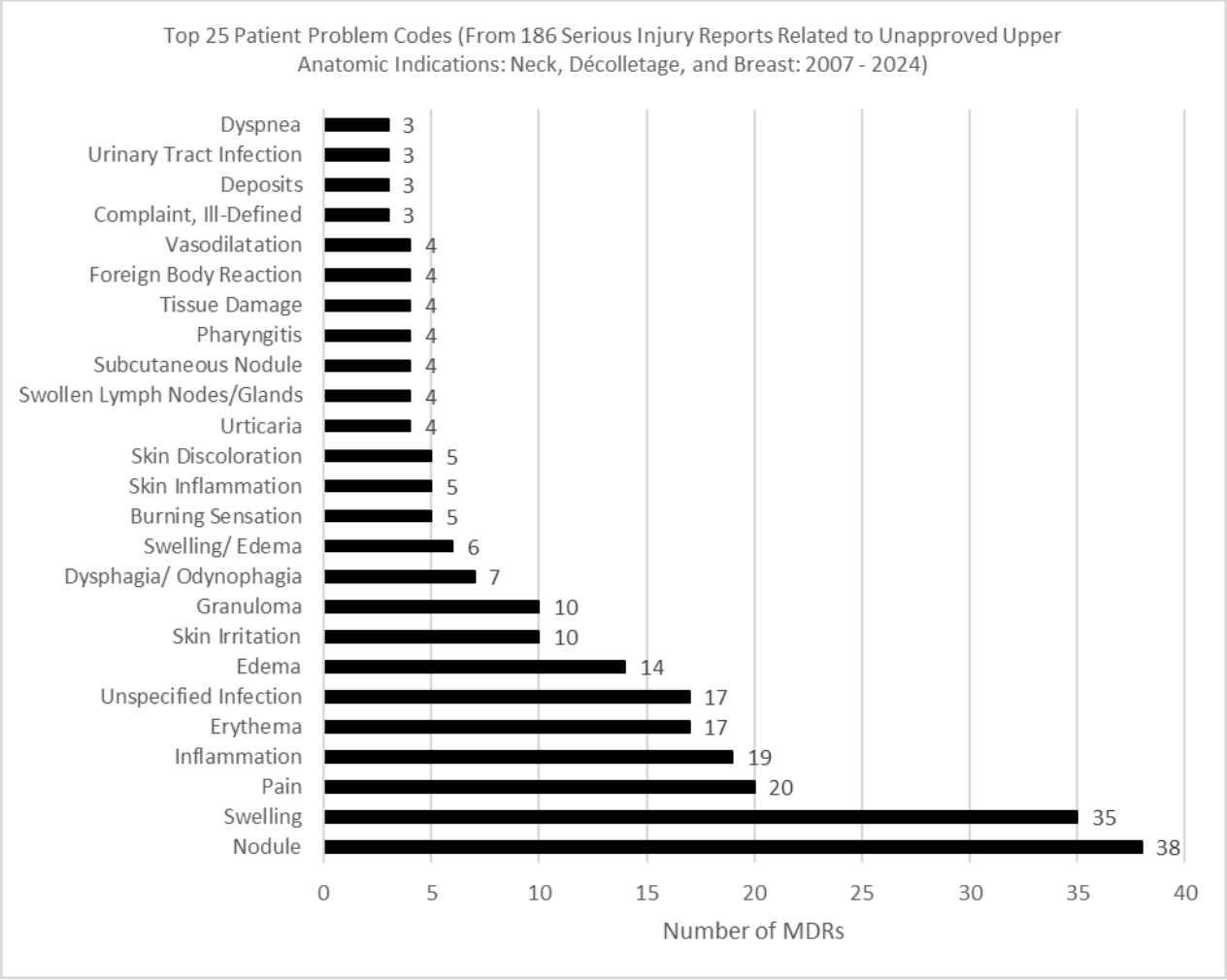

Figure 4. Top 25 Patient Problem Codes. Serious injury reports associated to dermal filler injections to unapproved upper anatomic indications including neck, chest/décolletage, and breast, from an all-time MDR search. For some of the reports, there was no code available (47), Appropriate Clinical Signs, Symptoms, Conditions Term / Code Not Available (49), and these were excluded from the Top 25 patient problem codes. Note that some reports listed multiple patient problem codes in a single MDR. This coding highlights some of the limitations of the MDR data.

A query of the unapproved upper body anatomic areas MDR reports for diagnostic imaging tests resulted in 43 MDRs. The search terms “imaging”, “MRI”, “PET”, “tomography”, “X-ray”, “ultrasound”, “mammogram”, “crystal”, “hypoechogenic”, “radiopaque”, “false positive”, and “calcifi” were used for the sub-analysis of Serious Injury MDR reports associated to unapproved upper body indications and their impact on diagnostic imaging tests. The search terms “hypoechogenic”, “radiopaque”, “false positive” yielded zero (n=0) results. Ultrasound was the most listed resulting in 28 MDRs. However, in most of these reports, ultrasound is used for guided removal of the filler with hyaluronidase. Of relevance, one of the MDRs relates to a literature article where high-resolution ultrasonography was used in the diagnosis of complications after dermal filler indication for facial contouring.

Systematic Literature Review (SLR) Related to Décolletage Indications

SLR identified 19 articles reporting use of a variety of fillers in décolletage, breast, or chest. This included 7 articles using CaHA fillers, 8 articles using HA fillers, 2 articles using PLLA, 1 article using liquid silicone (which has not been approved as a dermal filler in the U.S.), and 1 article using collagen filler. Other uses reported in these articles included use in the neck, in the hand, or for body contouring. Of these articles, 4 articles discussed radiological assessments, and, in each case, these subjects received injections of 100 ml to >200 ml of the fillers in question (3 articles HA fillers and 1 article liquid silicone). In Heden, et al, subjects were treated for pectus excavatum (mean volume 157 ml range 80-245 ml) and the study reported that at 12 months 67% of filler was visible on MRI and at 24 months 58% of filler was visible. Furthermore, in the Heden study, anticipated adverse events were reported; however, little information was available on the severity of AE observed [29].

In other articles, with use of CaHA fillers, 0.8-1.5 ml was administered, while HA fillers used 0.25 – 10 ml, PLLA 1-15 ml and collagen 1 ml. Generally, when these volumes were used, either no adverse events or anticipated adverse events (i.e. adverse events commonly observed with dermal filler injection such as swelling, bruising, and pain) were reported. However, not all articles were clear on severity or duration of reported AE. There was one report of accidental death in a study outside the US. The study reported using Fillamed HA filler in 49 female subjects in the décolletage. However, there were no details about the reported death which was deemed unrelated to the treatment [30].

Of note, the fillers in the décolletage and chest were as follows: CaHA filler studies enrolled a total of 233 subjects for treatment of the décolletage; HA filler studies enrolled a total of 162 subjects for treatment of the décolletage and 32 subjects for treatment of pectus excavatum; PLLA filler studies enrolled 35 subjects for treatment of the décolletage; liquid silicone studies retrospectively evaluated 3 patients with complications from silicone body contouring; and one collagen filler study enrolled 20 subjects (nipple projection).

Criteria for premarket assessment and mitigation strategies

Given the aforementioned risks and concerns associated with the use of dermal fillers in the décolletage, additional evidence is needed to establish a reasonable assurance of safety and effectiveness for the use of the device in the treatment of this anatomical location. For example, additional information regarding 1) breast cancer misdiagnosis, 2) diagnostic imaging interfering, 3) intravascular and lymphatic complications, 4) filler migration and the long-term influence on surrounding anatomy, either from real-world evidence or post-marketing surveillance for the use of the subject device in treatment of décolletage outside the US will help to further evaluate the risks of dermal fillers in the décolletage area.

Additionally, collection of any data (short and long-term) related to cross-sectional imaging of the breast (such as mammogram, ultrasound, MRI, and CT scan) during the course of the clinical studies, including any abnormal findings noted in the cross-sectional imaging and any additional tests or procedures performed in response to the abnormal findings will also be beneficial to evaluate these unique risks associated to the new intended use of dermal fillers and to minimize the uncertainty in the benefit/risk assessment for the device in the décolletage area.

Considering the risks unique to this anatomic location, FDA is proposing the following additional criteria to be incorporated in the premarket and/or post-market assessments for the patient subpopulation that may be candidate for injection into the décolletage area:

a. To assess for impact on imaging studies to screen or diagnose for breast cancer: Collection of baseline imaging (e.g., mammogram, ultrasound, or MRI), preferably within 2 years prior to injection and post-injection imaging.
b. To assess for migration of filler material to breasts or lymph nodes:
    - Premarket follow-up until quiescence of inflammatory response.
    - Post approval study on late-onset adverse events, effects on lactation and lymph nodes.
c. To mitigate and inform patients and providers about the potential risk in interference with radiographic studies:
    - Requiring that radiographic (e.g. mammogram, ultrasound, or MRI) images of the implanted device be included in the labeling.
    - Recommended device cards to be provided to patients and which may be included in patient records for dermal filler injections into the décolletage to help ensure that patients are aware that these dermal filler injections should be considered relevant procedures when undergoing mammography or other breast imaging and that future healthcare providers are adequately informed.

The panel will be asked about the proposed assessments and mitigation strategies for this new indication for use as well as for additional recommendations.

Removal of dermal fillers from the décolletage

After any dermal filler injection, there is a possibility that the device will need to be removed. This could be for safety reasons, such as unintended intravascular injection, impending necrosis, nodule formation, or for aesthetic reasons, such as overcorrection or undesirable clinical result. Removal or dispersion of injectable filler depends on the composition of the product.

A variety of management strategies have been proposed for intravascular injection, but no product has been approved by FDA for use for treatment of filler-related symptoms [10, 31-35]. Off-label use of hyaluronidase injection(s) is a clinically accepted method for removal of a hyaluronic acid filler [35]. Other options have been proposed including warm compresses, massage, nitroglycerin paste, aspirin, systemic steroids and intraarterial thrombolytic [10, 35]. For soft tissue necrosis, professional medical societies, such as the American Society for Dermatologic Surgery (ASDS), as well as expert panels have published guidelines of care for acute management [33-35]. For treatment of filler-related vascular occlusion with blindness, ASDS task force made conditional recommendation to strategies to reduce the risk of IRVC, however, safe and reliable treatment applicable to all fillers has not been identified [35]. 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 [7]. Health care practitioners are also encouraged to conduct vision assessments before and after treatment. 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. In clinical practice, dermal fillers are commonly injected without imaging guidance. Ultrasound examination with vascular mapping pre- and post-treatment has been suggested as a tool to optimize safety with injections [35, 36].

ASDS and other groups have published recommendations for the use of hyaluronidase for removal of hyaluronic acid-based dermal fillers as well as recommendations for some methods available for managing nodules caused by permanent and semi-permanent dermal fillers [35]. However, hyaluronidase

and other products have not been evaluated and approved by FDA for this use related to dermal fillers. Recommendations in literature for specific dosage and injection techniques have not been well established. Regulated as a drug, FDA-approved formulations of hyaluronidase are indicated for use as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs (e.g., local anesthetic in ocular surgery), and in subcutaneous urography for improving resorption of radiopaque agents. Although hyaluronidase has not been approved for use with dermal fillers, FDA has received 83 reports since 2011 of adverse events associated with this use including swelling, burning, redness, excessive loss of volume, and lack of effect as the most common reports.

For semipermanent fillers (PLLA, calcium hydroxyapatite) and permanent fillers (polymethylmethacrylate, silicone), there are no specific reversal agents (e.g., hyaluronidase for HA fillers). For treatment of nodules, there are reports of different methods (e.g. intralesional Kenalog and 5-fluorouracil) depending on the type of nodule. It has been suggested in the literature that in the case of nodules secondary to calcium hydroxyapatite, the clinician can consider sodium thiosulfate [35]. However, the safety and effectiveness of sodium thiosulfate for calcium hydroxyapatite nodule treatment and the potential for this approach to help remove calcium hydroxyapatite in the case of other complications (e.g. over correction and vascular occlusion) have not been thoroughly described. Sodium thiosulfate has not been approved by FDA for uses related to dermal fillers. Excision would be the final option for removal of these products [35]. FDA believes that conversations regarding the benefits and risks of removing dermal fillers may be best prior to injection.

If dermal fillers are injected into the décolletage, removal may become necessary – for example, if the device is interfering with imaging or cancer screening, impacting breast feeding, or affecting lymphatic drainage. Dermal filler removal methods have not been evaluated with a standardized approach for the different properties of new fillers or the different anatomy in new injection locations.

The panel will be asked if they have specific concerns related to the available removal options for dermal fillers if injected into the décolletage.

MDRs Related to Removal

A query for the removal of dermal filler implant material MDR reports for chemically induced removal/dispersion and physical removal resulted in 5,945 MDRs. MDR reports commonly list more than one removal approach and treatment for the overcorrection, nodule formation, intravascular injection, or other factors. The search terms “hyaluronidase”, “hylenex”, “hydase”, “amphadase”, “vitrase”, “reductonidase”, “vorhyaluronidase alfa”, “hylase”, “sodium thiosulfate”, and “excis” were used for the analysis of Serious Injury MDR reports where removal or dispersion of the implant material was needed. The search terms associated with hyaluronidase were the most listed resulting in 5,171 MDRs (5171/5966; 86.7%), while the use of sodium thiosulfate and surgical excision for removal of the device resulted in 53 (53/5966; 0.9%) and 742 (742/5966; 12.4%) MDRs. Note that some reports listed multiple treatments for removal of device in a single MDR. This highlights some of the limitations of the MDR data.

Figures 5 shows the breakdown of device removal by dermal filler composition. The most commonly listed dermal filler type in MDRs associated with the removal of the implant material is HA dermal fillers

in 5616/5945 (94.5%), followed by CaHA dermal fillers with 268/5945 (4.5%), and PLLA dermal filler with 68/5945 (1.1%) MDRs.

A breakdown of the top 35 problem codes for these 5,945 Serious Injury reports, for which removal or dispersion of the implant material was reportedly performed, is shown in **Figure 6**. Obstruction/Occlusion is one of the top serious adverse events reported (N=1,005). Other common serious adverse events include vascular impairment, necrosis, and ischemia.

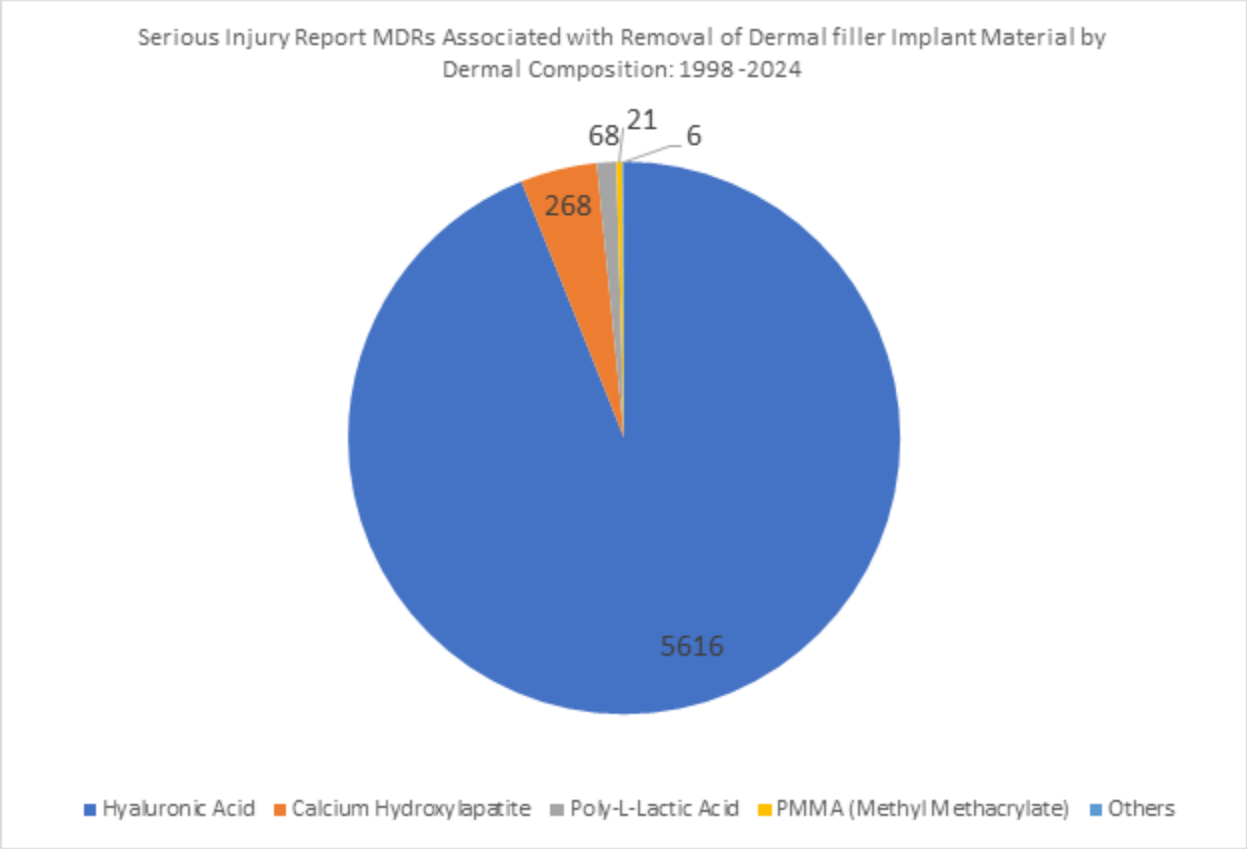

Figure 5. MDR Reports Associated with Removal of Dermal Filler Implant Material by Dermal Filler Composition. Serious Injury reports resulting from an all-time MDR search for the dermal filler product codes LMH.

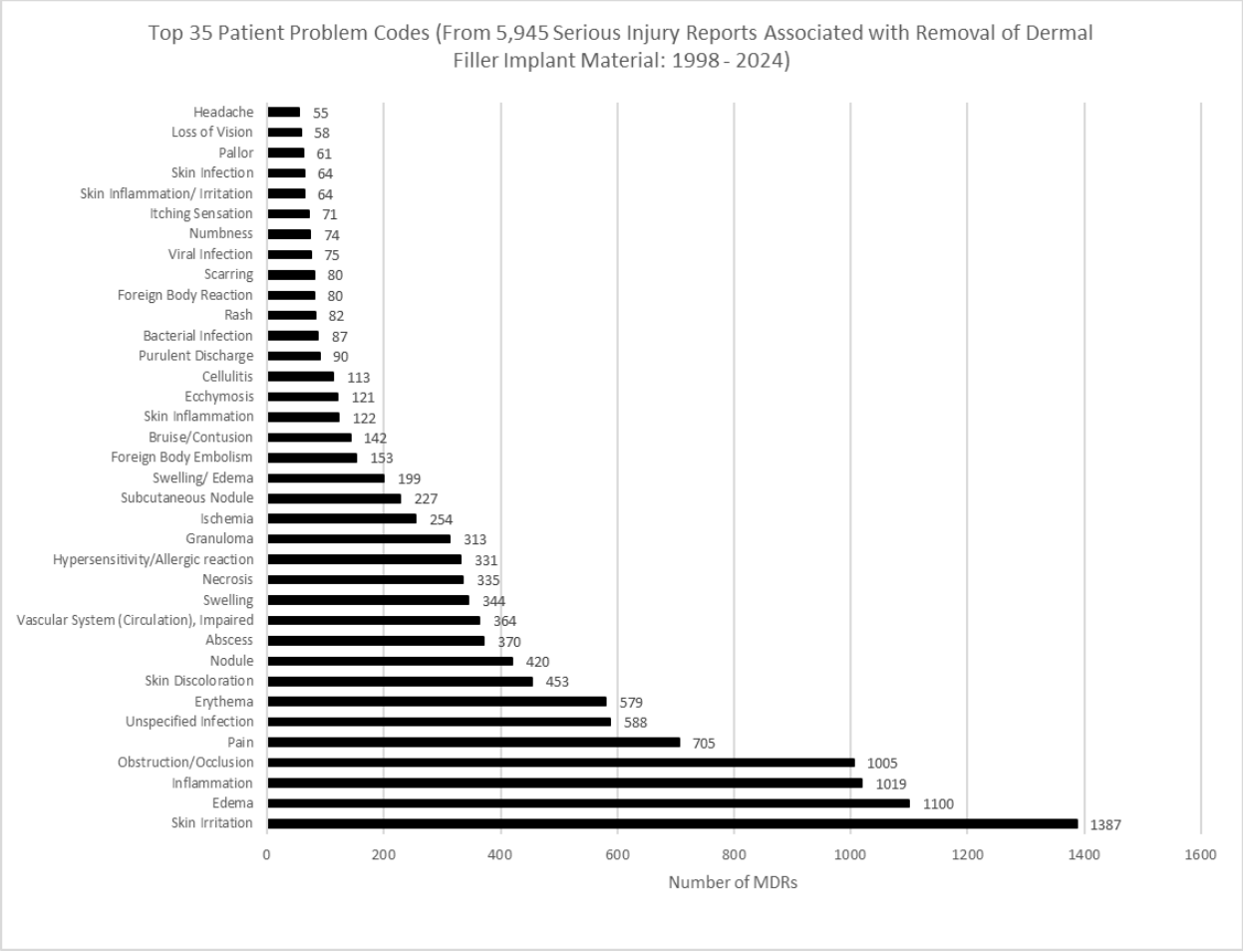

Figure 6. Top 35 Patient Problem Codes.

The most reported patient problem codes for the serious injury reports (N = 5,945; received for product codes LMH and PKY) for which removal or dispersion of dermal filler implant material were reportedly performed, from an all-time MDR search. For some of the reports, there was no code available (223), Appropriate Clinical Signs, Symptoms, Conditions Term / Code Not Available (176), and these were excluded from the Top 35 patient problem codes. Note that some reports listed multiple patient problem codes in a single MDR. This coding highlights some of the limitations of the MDR data.

Patient preference

Patient preference information (PPI) includes assessments of the desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions[37]. This information can be helpful to understand the value patients place on device features and different patient perspectives on the benefits and risks for given devices or procedures. Patient preference and informed decision making were previously discussed at the March 23, 2021, General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting[38]. FDA proposed the proactive incorporation of patient preference information into premarket clinical studies, and the panel recommended that a study evaluating safety and effectiveness of a device may not be the appropriate venue for the collection of this data [38]. While the panel acknowledged the

importance of this information, they also discussed challenges in collecting it, especially in a premarket clinical study.

The use of dermal fillers in new indications, such as the décolletage, brings new questions of safety discussed above that may affect the benefit-risk considerations for patients. As mentioned previously, there is a recommendation for breast cancer screening for women in the age bracket of 40 to 74 [25]. It is unclear whether injections of dermal fillers in the décolletage will impact mammography readings. If there is a potential for misinterpretation of mammography, this could pose a significant risk to patients treated in the décolletage.

Considering the unique risks associated with this aesthetic indication, it is important to understand the patients' perspective of these risks. FDA believes a patient preference study could inform a regulatory decision by obtaining information about how patients weigh or trade-off the potential benefits of using the device against the potential risks, such as interventions which could result from false positive breast screenings like mammogram, ultrasound, MRI, or biopsy. A preference study could estimate research participants weighting of the potential risks, and if they would be willing to accept the risks for the potential benefits of treatment with a dermal filler in the décolletage.

The panel will be asked to consider the risks identified in the prior questions and identify which key risks they would recommend for incorporating into a patient preference study to estimate the maximum risk that patients would be willing to accept for the potential benefits.

VI. Appendix

FDA Approved Dermal Fillers

Trade Name	Material	Applicant	PMA Number	Decision Date	Approved For
The following dermal fillers were approved between February 1, 2021 and May 28, 2025					
Evolysse Smooth, Evolysse Form	Hyaluronic Acid, Lidocaine	Symatese	P240022	2/13/2025	Dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as NLFs) in adults 22 years or older
RHA®3	Hyaluronic Acid, Lidocaine	Teoxane S.A.	P170002/S030	10/27/2023	Injection in the vermillion body, vermillion border and oral commissures to achieve lip augmentation and lip fullness in adults aged 22 years or older. Injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.
RHA® Redensity™ Mepi RHA® 2 Mepi RHA® 3 Mepi RHA® 4 Mepi	Hyaluronic Acid, mepivacaine	Teoxane S.A.	P170002/S026	10/13/2023	Approval of RHA® Redensity Mepi: Injection into the dermis and superficial dermis of the face, for the correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older.

					Approval of RHA®2 Mepi, RHA@3 Mepi: Injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older. Approval of RHA@4 Mepi: 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 (NLF), in adults aged 22 years or older.
JUVÉDERM® VOLUMA® XC	Hyaluronic Acid, Lidocaine	Allergan	P110033/S 070	10/06/2023	Injection to augment the temple region to improve moderate to severe temple hollowing in adults over the age of 21
BELOTERO BALANCE (+)	Hyaluronic Acid, Lidocaine	Merz Pharmaceuticals	P090016/S 050	09/27/2023	Improvement of the Infraorbital Hollow in Adults Over the Age of 21
SKINVIVE™ by JUVÉDERM®	Hyaluronic Acid, Lidocaine	Allergan	P110033/S 059	05/11/2023	Intradermal injection to improve facial skin smoothness of the cheeks in adults over the age of 21

Restylane® Eyelight	Hyaluronic Acid, Lidocaine	Q-Med AB/ Galderma Laboratories	P040024/S 135	05/08/2023	Improvement of infraorbital hollowing in patients over the age of 21
Sculptra	Poly-L-Lactic Acid (PLLA)	Q-Med AB/ Galderma Research & Development	P030050/S 039	04/18/2023	correction of fine lines and wrinkles in the cheek region for use in immune-competent subjects.
JUVÉDERM® VOLUX™ XC	Hyaluronic Acid, Lidocaine	Allergan	P110033/S 065	07/29/2022	Subcutaneous and/or supraperiosteal injection for improvement of jawline definition in adults over the age of 21 with moderate to severe loss of jawline definition
RHA® Redensity™	Hyaluronic Acid, mepivacaine	Teoxane S.A.	P170002/S 012	12/22/2021	Injection into the dermis and superficial dermis of the face, for the correction of moderate to severe dynamic perioral rhytids, in adults aged 22 years or older.
RADIESSE® (+) Lidocaine injectable implant	Hydroxyl-apatite, lidocaine	Merz North America	P050052/ S129	09/01/2021	Injection into deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve moderate to severe loss of jawline contour in adults over the age of 21
Restylane® Contour	Hyaluronic Acid, Lidocaine	Q-Med AB/ Galderma Laboratories	P140029/S 032	06/28/2021	Cheek augmentation and correction of midface contour deficiencies in patients over the age of 21

JUVÉDERM® VOLUX™ XC	Hyaluronic Acid, Lidocaine	Allergan	P110033/S053	05/28/2021	Improvement of infraorbital hollowing in adults over the age of 21.
The following dermal fillers were approved prior to February 1, 2021					
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 Hyaluronat e 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	Hyaluronic 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	Polymethyl m ethacrylate 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 Pharmaceutic als 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 Pharmaceutic als	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	Polymethyl m ethacrylate 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).
COSMODER M 1 COSMODER M 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.

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