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Fillers: From the Past to the Future

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Modern medical use of injectable soft-tissue augmentation fillers has evolved from the introduction of bovine collage implants to an array of synthesized materials in the current domestic and foreign markets. The concept of augmentation has moved from simple lines, scars, and wrinkles to revolumizing the aging face. A brief overview of the past, present, and future injectable fillers is presented.
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The evolution of injectable fillers in dermatology has been an organic process that began with one set of therapeutic goals and a single agent. It has morphed into a different set of goals with a burgeoning number of agents available to the cosmetic dermatologist. In the early 1970s, collagen was used for the treatment for lines, wrinkles, and scars. Although the Zyderm was the first FDA-approved commercial product, the way physicians looked at the target was very different from their view of the esthetic challenges in facial aging today. For example, there was no real distinction made between the crease of the nasolabial fold, the glabellar lines, rhytids above the upper lip, and sleep lines. All of these were seen as variations on alteration in dermal architecture.

The contribution of movement to the establishment of the dynamic lines of expression was really not fully appreciated until the advent of neurotoxins almost 20 years later, when, for the first time, it was possible to selectively remove the contribution of movement and analyze the components of intrinsic and extrinsic aging changes in the skin itself. The dramatic resolution of many dynamic lines with botulinum toxin actually stimulated interest in fillers, holding out hope that one could possibly obtain the same definitive results with fillers that were routinely seen with botulinum toxins. Thus, the stage was set for the evolution of facial aging analysis as the concept of volume came to the foreground.

With various techniques available to address the textural changes of photoaging (such as peels and lasers, dermabrasion), the use of superficial dermal fillers and botulinum toxin left many patients with less than satisfying results, even after surgical rejuvenation. Many patients in whom resurfacing that may or may not include lifting, relaxation or superficial fillers, were performed continued to look better, but not rejuvenated. Although the introduction of hyaluronic acid (HA) gel fillers was a turning point, the realization that using these fillers in the deeper compartments of the face, subcutaneous and deeper, brought startlingly subtle, yet definitive, rejuvenation to the patients' faces. We are now in the next phase of development regarding injectables: the third dimension. Although seeking extended duration of effect balanced against the safety profile of the injectable, our focus is directed to extending the lifting or volumizing effect that one can achieve with these fillers.

Of course, there is seldom something new that does not build on the past. The initial movement into 3-dimensional correction with injectable fillers began with the dramatic improvement seen in lip volume with the collagen fillers championed by Arnold W. Klein, MD, in the 1980s. This volume correction achieved in the lip far exceeded the impact of wrinkle and scar correction, and the impact on clinical practice was simply enormous. Experienced clinicians reported using almost half of their collagen products in lip augmentation for many years with great success. But clearly the lack of duration of the product and the inability to achieve significant volume correction with 1-mL syringes tempered the utility of volume correction with collagen in the non-lip areas—midface, temple, brow, and perioral tissue—where the newer fillers are much more effective. But the litany of fillers discussed later in this paper shows that each filler has come along at a different point as we moved from static lines to dynamic lines, to volume, and to the problem of 3 dimensions in the face.

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With the aging of the post–World War II boomers, the round full faces of youth have given way to the flat and hollow convexities of aging faces, and the need for volume replacement has never been more obvious, especially in areas of premalar, cheeks, midface, chin, jowl sulcus, cheek hollows, the brow, and so forth. But the industry seems stupefied by the inability to think "outside of the box." The incongruity of the 1-mL syringes that still dominate the marketplace is the prime example. The volume of filler originally designed to treat a single line/wrinkle is totally inadequate for the volume required for 3-dimensional filling. How did we arrive at this point? A cursory review of the development of injectable fillers for soft-tissue augmentation may give us some answers.

Fat as a Filling Agent

The modern era of fat transplantation followed the development of liposuction surgery in 1974 by Giorgio Fischer,[1] MD, in Rome, and in 1978 by Yves-Girard Illouz,[2] MD, and Pierre Fournier,[3] MD, in Paris. During the 1980s, Dr Fournier[4] began microlipoinjections in which 13-gauge needles attached to ordinary syringes were used to collect fat for transplantation. The overarching issue with fat transplantation was (and is) that longevity varied from patient to patient and even from site to site. Average fat survival rates appeared to range from 25% to 30% persistence when injected into the cheeks, forehead, and nasolabial folds. The procedure is cumbersome, requires local anesthesia, and is generally more time-consuming than using an off-the-shelf injectable filler agent. The attraction of fat as a filling agent faded in the late 1980s, but has recently received some attention with the current research into fat as a source of stem cells. However, in the 1970s, fillers first came of age with the first commercial filling agent of the modern era: collagen.

Collagen (Zyderm, Zyplast, Cosmoderm, Cosmoplast, Evolence)

Collagen implant material was first developed by 4 Stanford doctors in the early 1970s.[5] Zyderm 1 implant (35 mg/mL of solubilized collagen) was approved by the U.S. Food and Drug administration in 1981, and Zyderm 2 (65 mg/mL of solubilized collagen) was approved in 1983. Both products were a relatively nonviscous suspension that permitted injection through a 30-gauge needle. As of 1983, more than 10,000 patients had been treated with Zyderm collagen.

All forms of injectable bovine collagen are mildly immunogenic. The threat of bovine spongiform encephalopathy from prion disease mandated the use of closed herds as the only suitable source of solubilized collagen. Nonbovine collagen sources were developed from human tissue culture lines (Cosmoderm, Cosmoplast), which eliminated the delayed hypersensitivity reactions seen with the bovine products, but the very limited duration of effect (generally 3-4 months) and the desire to move away from protein-based fillers led to their gradual abandonment from the market once the HA gels arrived on the scene. But for 22 years, from 1981 to 2003, collagen was the only commercially available FDA-approved product in the U.S. market. The only other product that was in significant use during that period was silicone, which, because it was not approved by the FDA, has had a more checkered history.

Silicone

In 1959, the Dow Corporation introduced medical grade silicones—long polymers of dimethylsiloxanes, colorless, odorless, tasteless fluids whose viscosity varies according to degree of polymerization—to physicians.

In 1963, Dow developed a more purified medical grade 360 silicone (360 centistokes viscosity, noted to cause minimal inflammation in the subcutaneous tissue of human volunteers).

Complications from silicone were reported when large volumes of silicone were injected, notably paraffinoma-like granulomas. Dow soon developed a highly purified medical grade silicone called MDX 4-4011 but FDA-approved investigation halted in 1967, and in 1978, the FDA narrowed the scope of the study of silicone. In the 1970s and 1980s, several studies were published that purported the safety of the microdroplet technique.[6] Injection of minute amounts with a fine-bore needle was determined to be safe and effective, with very few adverse effects reported.[7,8]

However, there was no FDA-approved commercial product until the arrival of Silikon 1000, an ophthalmologic silicone oil with a viscosity of 1000 centistokes, approved in 1997 for use in postoperative retinal tamponade during vitreoretinal surgery. Many dermatologists use Silikon 1000 "off label" with the microdroplet technique for the treatment of acne scars, HIV lipodystrophy, traumatic fat atrophy, rhinoplasty defects, and some facial aging where volume repair gives an effective result.

Illegal use of adulterated industrial grade silicone fluids by unlicensed laymen continues to produce sensational adverse reactions including deaths, a reality that has colored the public's perception of this valuable tissue augmentation agent. Illegal use of non–medical grade product, together with the controversy surrounding silicone breast implants, has kept the use of silicone as a filler agent in the background for some time.[9] The lack of commercial sponsorship of necessary long-term safety studies virtually guarantees it will remain an "off-label" use in the foreseeable future. The explosive expansion of the commercially available fillers in the U.S. market came instead with the introduction of the HA gels in 2003.

Hyaluronic Acids (Restylane, Perlane, Juvederm Ultra and Ultra Plus)

HA is the main polysaccharide in human extracellular matrix tissue. It acts as a scaffold for collagen and elastin to bind. Because it binds to water, it augments and hydrates the skin,

and when used in commercial filler agents, it consists of repeating polymer chains of the polysaccharide with interval cross-links of agents that bind the polymers together. By varying the type of cross-linking material and the amount, the characteristics of the gel can vary in the degree of hardness, amount of lift, duration of survival, and resistance to degradation by heat or enzymes. At present, the source of the HA used in commercial products is bacterial, leading to the designation of this class of fillers as NASHA (non–animal-sourced HA gel), which distinguishes them from the earlier bovine- and human-sourced collagen products. Hyaluronic gel products can be found either as biphasic types in which varying-sized particles predominate or as monophasic types in which the HA is a homogeneous solution.

After years of use outside the United States, Restylane (Q-med, Uppsala, Sweden) became the first HA to enter the U.S. market with FDA approval in December 12, 2003, 9 months after the FDA approval of the Cosmoderm human collagen implants (see http://www.fda.gov/MedicalDevices). This was a watershed event that marked the end of 17 years of domination of the collagen products in the U.S. filler market. Restylane has an HA concentration of 20 mg/mL of HA with a gel bead size of 250 μM and 100,000 units per mL, and an estimated 0.5%-1.0% cross-linking with BDDE (butanediol diglycidyl ether). Perlane (Q-med, Uppsala, Sweden), which has been approved, is a 20 mg/mL of HA with a larger gel bead size of 1000 μM and 10,000 units per mL, and $<$1% cross-linking. Perlane is positioned as a more robust HA filler in the Q-med line.

The transitory presence of some fillers in the U.S. market can be illustrated by the fate of Hylaform (Inamed, Santa Barbara, CA), which the FDA approved in April 2004. Hylaform had 5.5 mg/mL of HA and 20% cross-linking with divinyl sulfone. Hylaform Plus (Inamed, Santa Barbara, CA), approved on October 13, 2004, had 5.5 mg/mL, larger gel particle size, and 20% cross-linking. Both products were HA gels derived from rooster cockscombs; the products were withdrawn because of the consumers' preference to move away from animal-sourced products and the lack of duration of effect of the less-concentrated Hylaform. In addition, the manufacturer of Hylaform, Inamed, was acquired by Allergan in 2006. Allergan had distribution rights of the competitive HA filler, Juvederm, which is manufactured by Corneal Laboratories (Pringy, France). Allergan then completed its purchase of Corneal in January 2007, leaving no further purpose for Hylaform in the Allergan portfolio.

HA fillers as a class have become the most popular filler in the U.S. market and, in one form or another, worldwide. They are reversible with hyaluronidase, an important safety consideration. They provide more immediate "lift" than the collagens, last much longer, and require no allergy skin testing before treatment. They can be easily injected through a small-gauge needle, and they eliminate the problems of products that use animal-derived protein. As a result, they have virtually eliminated collagens from the market. In fact, at the time of writing this article, no commercially available injectable collagen products were available in the U.S. market.

Poly-L-Lactic Acid (Sculptra)

The FDA accepted "non-inferiority" comparative trials to evaluate the fillers that came after collagen. Perhaps as result of these clinical trial designs, manufacturers continued to present the marketplace with single syringes of approximately 1.0 mL in volume. However, the HIV epidemic created a compelling need for volume restoration because of the pan-facial atrophy associated with HIV/AIDS and protease inhibitor therapies. The FDA approved poly-L-lactic acid (PLLA) (Dermik, Laboratories, Berwyn, PA) in August 2004 for the correction of facial atrophy, secondary to HIV and therapy for AIDS. Off-label use for areas such as the nasolabial folds began almost immediately. The FDA then granted a second approval for treatment of nasolabial folds and facial wrinkles to the sponsor, Sanofi-Aventis U.S., in August 2009. PLLA is a filler, with duration reportedly lasting as long as 18-24 months. It requires that the filler be prepared in advance using sterile preserved water and that the patient come in for a minimum series of 3 injections over the course of several months. The poly-L-lactic material is thought to stimulate fibroblasts in the host to produce collagen. Although the PLLA continues to have its advocates, the initial failure to appreciate the need for dilution before use to avoid lumps, lack of reversibility, and dependence on multiple treatments to achieve results have limited wider use of the product. The desire to achieve "permanent" results has spurred the introduction of other products, which promise, and occasionally deliver, the possibility of longer durations, including fillers that contain particles that resist biological degradation, such as calcium hydroxylapatite and polymethyl methacrylate (PMMA).

Calcium Hydroxylapatite (Radiesse)

Calcium hydroxylapatite (Radiesse, now owned by Merz Aesthetics, formerly BioForm Medical, Wisconsin) was approved by the FDA on December 22, 2006, for the augmentation of moderate to severe facial lines and folds and for facial soft-tissue loss from HIV-related lipoatrophy. It consists of 30% concentration of 25-45-μm calcium hydroxylapatite spherical particles suspended in sodium carboxymethylcellulose (CMC) gel. It lasts approximately 1 year or more in most patients. It is inherently biocompatible because it is identical in composition to bone material. Off-label use has included volume restoration for dorsal hands and postrhinoplasty contour correction. Lack of immediate reversibility and contraindication for use in the lips limit applicability to some extent, but the product has a steady niche market.

Polymethylmethacralate (Artefill)

PMMA is composed of nonresorbable PMMA 20% and 80% bovine collagen and was approved by the FDA as

Table 1 Classification of Non-permanent Fillers in the U.S. Market According to Source Material

Nonpermanent Fillers—U.S. Market			
Collagen			
Human	Animal	Hyaluronic Acid Gels	Synthetics
Cadaver Donor	Bovine	*Captique	Poly-L-Lactic Acid
Alloderm	*Zyderm 1, 2	*Hylaform	
Cymetra	*Zyplast	*Hylaform Plus	
*Fascian	Porcine	Elevess (Hydrelle)	
*Dermalogen		Prevelle Silk	
Autologous	*Evolence	Juvéderm Ultra	
	*Fibrel	Juvéderm Ultra Plus	
Dermal grafts		Juvéderm XC	
*Autologen		Perlane, Perlane-L	
		Restylane, Restylane-L	Sculptra
Bioengineered Human		Belotero Balance	Sculptra Aesthetic
*Cosmoderm I, II			Cacium hydroxylapatite
*Cosmoplast			Radiesse

*No longer commercially available in the United States.

Artefill in October 2006 (Artes Medical, San Diego), following earlier European use as Artecoll, dating back to 1998. After corporate upheaval involving the original management under the founder, Gottfried Lemperle, the product was purchased out of bankruptcy in 2009 by Cowen Healthcare Royalty Partners and reorganized as Suneva Medical.[10] Artefill is a chemically inert and biocompatible synthetic implant used in bone and dental implants. Skin allergy prescreening tests are needed because of the bovine collagen carrier. The body degrades the collagen carrier within 1-3 months. The PMMA microspheres are nonbiodegradable, and their persistence is extremely long-lasting to permanent. The use of PMMA is appropriate for patients with well-defined deep facial wrinkle lines. Granulomas appear to be less common with the current product, down to 0.01% range, but issues of sensitivity to the bovine collagen component and the animal derivation of the collagen remain. Clinical trials for acne scarring are reportedly underway after reports of utility in this indication.[11]

The Future

The current status list of fillers in the U.S. market can be subdivided on the basis of biodegradability and duration of effect (Tables 1 and 2). The classification reflects only those products that were, or are, commercially available in the U.S. market. In contrast, the list of filler products that are commercially available outside of the United States is protean. There are more than 200 commercial products outside the United States, and the list presented in Table 3 is only a partial selection, chosen for their widespread use outside the United States or for their representation of new classes of fillers.

Although admittedly many of these are refinements of existing technologies (eg, HA gels with better cross-linking, different particle size, combined with anesthetic agents), many are new classes of products that differ from those currently available in the United States (eg, polyacrylamide gels, cross-linked dextran, CMC, hypromellose). Two of these are examples that illustrate how these agents may be expected to evolve the market further: Contura's Aquamid (Contura International A/S, Denmark) and Ellansé by Aqtis (Aqtis Medical BV, Utrecht, The Netherlands) (Figure 1).

Aquamid is a bio-compatible, nonabsorbable, permanent injectable implant currently under FDA review. It is a so-called hydrogel, made of 97.5% water and 2.5% polyacrylamide gel. It has been used in Europe with 5-year prospective follow-up data. Although it fulfills the consumer's desire for permanence, it is nonreversible. Therefore, when the rare problem of delayed infection occurs, it can be important to recognize and manage the complication promptly before a chronic situation develops. The role of biofilm formation in the development of delayed infections has been proposed, but the manufacturer suggests that "The hydrogel exchanges water with the surrounding tissue, preventing biofilm formation."[12] It is important to recognize that this material pro-

Table 2 Classification of Permanent Fillers in the U.S. Market According to Source Material

Permanent Fillers		
Particulate	Silicones	Expanded PTFE Implants
ArteFill	Silikon 1000	Gore-Tex
	Adatosil 5000	*Ultrasoft
		*Softform
		Surgisoft (Advanta)
		VeraFil
	Fat	Classification of Soft-Tissue Implants
		Temporary: 0-6 months
	Autologous fat	Semipermanent: 6 months-2 year
		Permanent: >2 years

*No longer commercially available in the United States.

Table 3 Partial List of Injectable Fillers Commercially Available Outside the United States

Manufacturer	Device	Class/Type	Concentrations/Characteristics	Approval/Availability
Allergan	CosmoDerm	Purifed human-based	Purified human-based collagen 35 mg/mL	Worldwide
	CosmoPlast	Collagen + lidocaine	Purified human-based collagen 35 mg/mL, cross-linked with glutaraldehyde—both contain 0.3% lidocaine	Worldwide
	HydraFill - Softline	Non-animal stabilized hyaluronic acid (NASHA)	NASHA 24 mg/g	CE
	HydraFill - Softline Max		NASHA 24 mg/g	CE
	Surgiderm 18	NASHA	NASHA 18 mg/g	CE
	Surgiderm 30		NASHA 24 mg/g	CE
	Surgiderm 24XP		NASHA 24 mg/g	CE
	Surgiderm 30XP		NASHA 24 mg/g	CE
	*Juvéderm Ultra Smile	NASHA	NASHA 24 mg/g	CE
	*Juvéderm ULTRA 2		NASHA 24 mg/g	CE
	*Juvéderm ULTRA 3		NASHA 24 mg/g	CE
	*Juvéderm ULTRA 4		NASHA 24 mg/g	CE
	*Juvéderm VOLUMA		NASHA 20 mg/g	Worldwide and FDA pending
	*Juvéderm HYDRATE		NASHA 13.5 mg/g + mannitol, 0.9%	CE
Anteis S.A.	Esthélis soft	NASHA	NASHA 20 mg/mL	CE
	Esthélis basic	NASHA	NASHA 22.5 mg/mL	CE
	Fortélis extra	NASHA	NASHA 25.5 mg/mL	CE
	Modélis shape	NASHA	NASHA 26 mg/mL	CE
	Mesolis	NASHA	NASHA non–cross-linked 14 mg/mL	CE
	Mesolis+	NASHA + glycerol	NASHA non–cross-linked 18 mg/mL + glycerol	CE
Aqtis medical	Ellansé (-S, -M, -L, -E)	Poly-caprolactone (PCL)	PCL 25-50- μm smooth particles homogenously suspended in an aqueous carboxymethylcellulose (CMC) gel-vehicle	CE
BioPolymer GmbH	MATRIDEX	Hyaluronic acid and diethylaminoethanol (DEAE) Sephadex	MATRIDEX: synthetic hyaluronic acid sodium salt 25 mg, hypromellose 15 mg, positively charged DEAE sephadex particles 25 mg (cross-linked dextran)	CE No FDA approval
	MATRIDUR		MATRIDUR: synthetic stabilized hyaluronic acid sodium salt 25 mg and hypromellose 5 mg	
	MATRIGEL		MATRIGEL: stabilized HA 12.25 mg	

Table 3 Continued

Manufacturer	Device	Class/Type	Concentrations/Characteristics	Approval/Availability
Contura International	Aquamid	Polyacrylamide gel	2.5% cross-linked hydrophilic polyacrylamide gel (PAAG) and 97.5% nonpyrogenic water	CE
	Aquamid reconstruction			Pending FDA approval
Filorga laboratoires	X-HA3	NASHA	NASHA 23 mg/mL	CE
	X-HA volume	NASHA	Same as above	CE
	M-HA18	NASHA + glycerol	NASHA (18 mg/mL) + glycerol (20 mg/mL)	CE
	NCTF135	NASHA + various ingredients	NASHA (0.025 mg/mL) plus vitamins, amino acids, coenzymes, minerals, nucleic acids	CE
	NCTF135H	NASHA + various ingredients	NASHA (5 mg/mL) plus vitamins, amino acids, coenzymes, minerals, nucleic acids	CE
Galderma	EMERVEL	NASHA	NASHA 20 mg/mL	CE
	Restylane	NASHA cross-linked with BDDE	Restylane - 100,000 particles per mL	Restylane worldwide
	Restylane Touch		Restylane Touch - 500,000 particles per mL	Except Japan
	Restylane Perlane		Restylane Perlane - 10,000 particles per mL	Perlane, Sub-Q and Touch worldwide except Japan and United States
	Restylane Sub-Q		Restylane Sub-Q - 1000 particles per mL	
	Restylane Lipp			FDA pending Restylane Lipp CE
	Restylane Vital		Concentration 20 mg/mL, homogeneous, sans particles	
	Restylane Vital Light		Concentration 12 mg/mL, homogeneous, sans particles	
	Macrolane VRF30 Macrolane VRF20		1000 particles per mL	
LCA pharmaceutical	Hyaluderm	Hyaluronic acid	Hyaluderm—non–cross-linked sodium hyluronate, 2.0%-2.5%	CE. No FDA approval
MD skin solutions	Pluryal	Monophasic and reticulated nonanimal	Pluryal: concentration 23 mg/mL—normal viscosity, versatile filler for wrinkle correction	CE
	Pluryal volume	Hyaluronic acid	Pluryal volume: concentration 23 mg/mL—high viscosity, filler for volume creation, and deep deficit correction	
MedizinSysteme	ZFill refresh	NASHA	NASHA (BDDE)	CE
	ZFill deep		NASHA (BDDE)	
	ZFill repair		NASHA (BDDE)	

Table 3 Continued

Manufacturer	Device	Class/Type	Concentrations/Characteristics	Approval/Availability
Merz Pharmaceuticals GmbH	Belotero Soft 20 mg/mL Basic 22.5 mg/mL Intense 25.5 mg/mL Balance 22.5 mg/mL	Hyaluronic acid	Non–animal double-phase cross-linked HA—via biofermentation—with CPM (Cohesive Polydensi_ed Matrix) technology	CE Belotero balance approved by the FDA for United States in November 2011
	Radiesse	Calcium hydroxylapatite (CaHA)	Synthetic calcium hydroxylapatite (CaHA- 55.7%) micro-spheres, 25-45 μm, suspended in an aqueous polysaccharide gel (1.3% sodium CMC USP, 6.4% glycerin USP and 36.6% water USP).	Radiesse FDA approved and CE in Europe
Polymekon	BIO-ALCAMID - face BIO-ALCAMID - lips BIO-ALCAMID - body	Polyacrylamide	BIO-ALCAMID—96% water and 4% synthetic reticulate polymer. Lips are soft and compact. Face has the same composition (it is not a dilution), body has the same consistency as the face form, but contains more material	CE in 2001, no FDA approval
	Bioinblue - lips Bioinblue - deepblue	Polyvinyl alcohol (PVA)	Bioinblue—PVA (polyvinyl alcohol 8%) and water (92%).	Bioinblue—CE 2003 no FDA approval.
Sanofi-Aventis	Sculptra - U.S., also known as New-Fill or New-Filla	PLLA	PLLA hydrogel belonging to the family of aliphatic polyesters. Synthesized from corn.	FDA has approved Sculptra as the only product for the restoration and/or correction of the signs of facial fat loss (lipoatrophy).
	Succeev	Hyaluronic acid		Approved in Europe in 2000 as NewFill – 2004 as Sculptra for facial esthetic use. Available in Europe, Asia and South America
TEOXANE laboratories	Teosyal family Ultimate Ultra deep Kiss Deep lines	NASHA	NASHA	CE, Canada, 70 countries worldwide

Table 3 Continued

Manufacturer	Device	Class/Type	Concentrations/Characteristics	Approval/Availability
	Touch up Global action First lines Meso			
	Teosyal PureSense family	NASHA + lidocaine	NASHA + lidocaine	CE, Canada, 15 countries worldwide, 60 more pending
	Ultimate Ultra deep			Not yet FDA-approved
	Kiss Deep lines Touch up Global action First lines			
	Teosyal Redensity R1	NASHA + lido + Dermo-restructuring complex	NASHA + lidocaine + 8-amino acids, 3-antioxidants, 3-minerals	CE, Canada, 15 countries worldwide, 60 more pending Not yet FDA-approved
Trillium Meditec, Inc, ONT, Canada (formerly ProCytech SA, France)	Outline fine Outline original Outline ultra	Polyacrylamide co-DADMA	Outline is absorbable polyacrylamide co-DADMA gel	Approved in Europe Not approved in the United States
	Evolution	Polyacrylamide	Evolution is a mixture of microscopic soft spheres of polyvinyl in a viscoelastic gel of polyacrylamide co-DADMA gel.	
VIVACY Laboratoires	STYLAGE S, M, L, XL STYLAGE special lips	Non–animal hyaluronic Acid IPN-like + antioxidant agent (mannitol)	Biodegradable, single-phase, cross-linked HA-based gels of non–animal origin with an innovative cross-linking technology	CE
	STYLAGE hydro STYLAGE hydromax	Non–animal hyaluronic Acid IPN-like + antioxidant and hydrating agent (sorbitol)	IPN-like (interpenetrated networks) incorporating natural antioxidants, mannitol and sorbitol	
	STYLAGE M lidocaine STYLAGE special lips lidocaine	Non–animal hyaluronic Acid IPN-like + Mannitol + 0.3% lidocaine		

CE, European CE mark; FDA, Food and Drug Administration.
*All Juvéderm ULTRA products contain 0.3% lidocaine.

Figure 1 (A and B) Examples of only two products pursuing FDA approval. The first is a polyacrylamide gel, Aquamid, which is a permanent injectable polyacrylamide gel implant. The second contains polycaprolactone smooth microspheres suspended in an aqueous carboxymethylcellulose gel vehicle. There will be many more fillers pursuing approval in the U.S. market to be sure.

duces its volume correction through the spatial volume of the material itself, not through a tissue stimulatory effect like PLLA, calcium hydroxylapatite, or even the NASHA fillers. So overcorrection in injection technique is absolutely contraindicated. Clearly one of the issues with this product will be who is administering it. Scrupulous attention to injection technique and hygiene, knowledge of anatomy, and restraint on the part of the patient and the clinician alike would seem to be most important if the material is to be used safely. As with all permanent fillers, the overriding issue is the identification of the true incidence of adverse effects and how they are managed. But the allure of permanent correction will likely continue to push this product forward.

Ellansé is composed of microspheres of polycaprolactone (PCL) suspended in a CMC carrier. PCL is a common material used in surgical sutures, such as Vicryl, Monocryl, wound dressings, and surgical mesh. CMC is found in fillers like Laresse (FzioMed USA, Santa Barbara, CA), Sculptra, and Radiesse, as well as wound dressings like Aquacel (Convatec, Skillman, NJ). The manufacturer proposes that the microspheres of the PCL are completely smooth and totally biodegradable over time, the rate being dependent on the length of the polymer chains of PCL in the microspheres at the time of implantation. The shorter chains are degraded more quickly than the longer chains, giving the opportunity to control the clinical duration of effect by shortening or lengthening the polymer chains. The product is available in versions S, M, L, and E, with durations of effect ranging from 1 to 3 years. The most immediate perioperative adverse event appears to be edema occurring in approximately one-third of the patients. The product is in use in Europe and is expanding to the Middle East and other areas. It is not approved by the FDA and has no commercial presence in the United States. Although it is not a reversible product like the HAs, it appears to claim a middle ground for duration between the HAs and the permanent fillers. We would expect to hear more about this product in the near future, and clinical experience accumulates in Europe.

However, it is possible that we shall see fillers moving beyond the traditional concept of inert medical devices into the realm of true biologics, materials that will improve the texture, elasticity, radiance, and possibly color, of the skin itself. Just as the last 40 years have seen the movement from 2 to 3 dimensions, the next 2 decades will see movement from the macro to the micro level, and fillers will become systems for active metabolic manipulation and protection of the aging skin. The challenge for us, as clinicians, will be to sort through the hype and be able to choose the products that will offer the balance of risk and benefit. Given the preternatural attraction of the public for the newest and the greatest, we will have our work cut out for us.

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