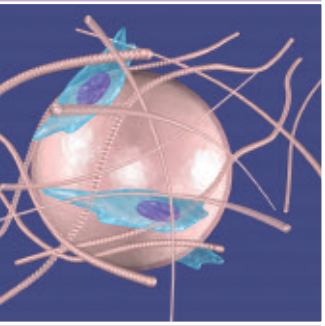
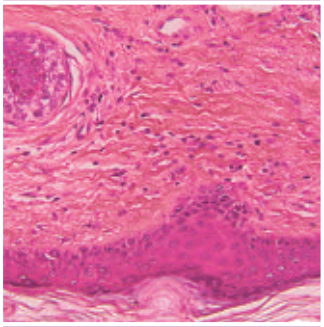
The Dermal Fillers Revolution





By Michael Moretti, Editor and Scott Greenwood, Contributing Editor

Market demand for new dermal filler materials has created a burgeoning industry populated by a rapidly growing number of manufacturers attempting to cash in on this trend. Consumer marketing combined with improved materials and injection techniques are expanding procedure volume at an unprecedented rate. As a result, aesthetic practices are increasingly reaping the rewards of nearly $2 billion in procedure fees, while satisfying our culture's insatiable need for enduring beauty.

The global market for aesthetic procedures is set to continue the extraordinary growth of recent years. According to the *American Society for Aesthetic Plastic Surgery* (ASAPS), approximately 23,000 dermatologists, plastic surgeons and cosmetic surgeons in the United States performed more than 11.8 million surgical and non-surgical cosmetic surgery procedures in 2004, generating $12.5 billion in fees. Already, the wholesale global dermal fillers market is estimated to be worth over $450 million as of 2005, a growth of over 200% since 2000. Growth in the U.S. dermal filler market is projected to expand at a compound annual rate of more than 25% during the next five years in the U.S., and 20% throughout the world.

There are now over 30 companies of significance offering more than 75 noted dermal filler products worldwide. In the U.S., only nine filler products are currently FDA approved for aesthetic indications (Zyderm 1, Zyderm 2, Zyplast, Cosmoderm, Cosmoplast, Hylaform, Hylaform Plus, Captique, Restylane), marketed by two companies (Inamed and Medicis), with three other filler products being used off-label for aesthetic indications – Radiesse, Sculptra, and Silikon 1000. The total number of approved products is expected rise to nearly 20 fillers, marketed by eight companies by 2007, as more products obtain FDA approval. One of the ASAPS' top ten predictions for 2006 accurately represents this trend: "the growth and popularity of cosmetic fillers will dramatically increase as products continue to evolve and new players enter the market."

Consolidation will be a highlight over the next few years as major consumer products, medical device and pharmaceutical companies continue to develop and acquire dermal filler brands to obtain entrance into or further penetrate the booming dermal filler market. This has become very clear with the recent purchase of Inamed by Allergan and with Mentor Corp.'s bid, in late 2005, to acquire Medicis.

Fueling the dermal filler market expansion is the aging population, more disposable income, increased awareness, improved technology, expanding social acceptance, and increased vanity. In regards to filler choices, what is gaining momentum amongst physicians and patients is the desire for non-animal, longer lasting fillers that provide an expedited, safe, comfortable, cost-effective natural correction. Any company that can provide a significant proposition which addresses these requirements will certainly gain market share.

Today, dermal fillers are being classified in three categories; temporary biodegradable, semi-permanent biodegradable, and permanent non-biodegradable filler materials. ***(See Figure 1 and Figure 2)***

Leading experts are also beginning to classify fillers via their mechanism of action; Volumizers, volume fillers, and Stimulators, tissue stimulating agents. Volumizers increase volume and fill out skin directly. Stimulators can also directly create volume, but primarily cause a foreign body reaction over a limited time, stimulating a long-term or permanent collagen deposition. Some fillers exhibit both actions and fall into both categories. ***(See Figure 3)***

Temporary Biodegradable

Collagen – Bovine, Porcine, Human

The demand for bovine collagen fillers is declining rapidly, due primarily to the emergence of new non-animal filler options, such as non-animal stabilized hyaluronic acid (NASHA), which has effectively met the increasing patient demand for same day,

Temporary biodegradable < 1 Year	Semi-permanent biodegradable 1-2 Years	Permanent non-biodegradable 2 > Years
Collagen – Bovine	CaHA – Calcium Hydroxylapatite	PMMA – Polymethylmethacrylate
Collagen – Human	DEAE – Sephadex particles (Dextran)	PAAG – Polyacrylamide Gel
Collagen – Porcine	PLLA – Poly-L-lactic Acid	LIS – Silicon (polydimethylsiloxane oil)
Hyaluronic Acid – Avian	PVA – Polyvinyl Alcohol	
Hyaluronic Acid – Bacterial	Chitosan	
	HEMA – Hydroxyethylmetacrylate	
	Cultured Human Fibroblasts	

Figure 1

Temporary biodegradable < 1 Year	Semi-permanent biodegradable 1-2 Years	Permanent non-biodegradable 2 > Years
Zyderm 1 & 2 / Zyplast	Radiesse	Artefill
Cosmoderm / Cosmoplast	Sculptra / New-Fill	Artecoll
EVOLENCE	Isolagen*	Silikon 1000™
Restylane / Touch / Perlane / Sub-Q	Reviderm	Aquamid / Aquamid Reconstruction
Hylaform / Fine Lines / Plus	MacDermol R	Amazingel
Captique	MATRIDEX	Dermalive / Dermadeep
Puragen / Puragen Plus	BioniBlue – Lips / DeepBlue	BIO-ALCAMID – Face / Lips / Body
Juvederm – 18 / 24 / 30 / 24hv / 30hv	Outline – Original / Fine	Evolution
Hydrafill – 1 / 2 / 3 / Softline	Fascian	Outline – Ultra
Surgiderm 18 / 30 / 24xp / 30xp / Lips	HylaDex	Beautical 2 / Beautical 5
Esthélis – Soft / Basic / Men / Duo		
Teosyal – 27G / 30G		
Rofilan		
Belotero – Basic / Soft		
MacDermol S		
MATRIGEL		
HylaNew / HylaNew Ultra		

Figure 2

non-animal, longer lasting dermal enhancement. Bovine collagen still has remaining benefits; the inclusion of lidocaine, the familiarity amongst practitioners and patients, history of safety, and lower cost. The launch of newer human and porcine collagen options are now on the market, and will eventually dominate the collagen segment.

Inamed (Santa Barbara, Calif.), with more than 20 years of providing safe and effective collagen treatments, has the most diverse and experienced portfolio of collagen dermal fillers among all companies. Their portfolio consists of three bovine collagen fillers – Zyderm™ 1 & 2 and Zyplast™, and two human derived collagen fillers – CosmoDerm™ and CosmoPlast™.

Zyderm I, Zyderm II and Zyplast, are composed of bovine collagen, harvested from a closed herd in Northern California, and mixed with sterile saline and a local anesthetic lidocaine, all three require skin testing four weeks prior to use. Zyderm l is used for very fine lines and Zyderm II is more concentrated and used for deeper wrinkles. Zyplast is stabilized and cross-linked

Border and smile before Tx

Border and smile after Zyderm/Zyplast Tx

Colbar

Volumizers	Stimulators
Collagen – Bovine, Porcine, Human	PLLA – Poly-L-lactic acid
Hyaluronic Acid – Avian / Fermented Bacteria	HEMA – Hydroxyethylmetacrylate
CaHA – Calcium Hydroxylapatite microspheres	CaHA – Calcium Hydroxylapatite microspheres
PAAG – Polyacrylamide Gel	PVA – Polyvinyl Alcohol
PMMA – Polymethylmethacrylate	PMMA – Polymethylmethacrylate
LIS – Silicon (medical grade polydimethylsiloxane oil)	DEAE – Sephadex particles (Dextran)
	Chitosan
	Cultured Human Fibroblasts

Figure 3

with glutaraldehyde, and ideal for deeper tissue defects. Zyderm I or Zyderm II may be layered more superficially after Zyplast, which is injected deeply into the dermis. Bovine collagen is metabolized fairly quickly, within about four months. The frequency of treatment required to maintain the desired augmentation can lead to a drop out rate of nearly 75% over time. The 28 day wait period required for allergy testing, may affect patient return due to buyers remorse. Another limiting factor is the pervasive issues surrounding animal sourced materials. These issues translate into Zyderm and Zyplast fast becoming sidelined by longer lasting non-animal based alternatives that do not require allergy testing.

Nasolabial folds and lip lines before Tx

Nasolabial folds and lip lines after CosmoDerm/CosmoPlast Tx

Before Tx

After EVOLENCE Tx

One of Inamed's answers to these issues is the recent launch of CosmoDerm and CosmoPlast – the only FDA approved dermal fillers in the world that contain bio-engineered type I/type III human collagen, with phosphate-buffered saline and 0.3% lidocaine. CosmoDerm and CosmoPlast do not require a skin test – allowing for same day treatment. CosmoDerm, which is non cross-linked, is best injected into the superficial dermis, and over correction of 100% – 200% is practiced.

CosmoPlast, which is cross-linked with glutaraldehyde, can be used to treat deeper lines or scars, and is best injected into the mid-to-deep dermis. Layering of CosmoDerm over CosmoPlast can be performed to eliminate a wrinkle or scar with no over correction. Results are slightly longer lasting than Zyderm/Zyplast at three to six months, although, some may have an aversion to the use of cadaver derived products.

The latest entrance into the collagen market is EVOLENCE™ from ColBar LifeScience Ltd. (Herzliya, Israel). Rona Steinberg, vice president of the aesthetics business unit of ColBar LifeScience Ltd., explains, "EVOLENCE is a new, porcine collagen-based, soft

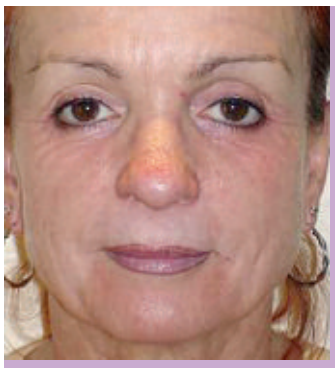
tissue filler that quickly and effectively restores shape to facial wrinkles – with benefits lasting for at least 12 months." According to Rhoda Narins, M.D., clinical professor of dermatology, New York University Medical Center, private practice in White Plains, N.Y., and past-president of the *American Society for Dermatologic Surgery*, "EVOLENCE could very well replace Cosmoplast as the longer lasting non-bovine collagen alternative. This filler is currently in clinical trials in the U.S. and results can still be seen anywhere from 12 to 18 months."

Ms. Steinberg continues to explain, "EVOLENCE has taken the established safety profile of collagen and has overcome rapid biodegradability through a novel cross-linking procedure. EVOLENCE is produced *in vitro* by polymerization of monomeric porcine tendon collagen followed by glycation with the natural sugar ribose, which unlike many cross-linking technologies does not require the use of potentially irritating chemicals which limit the degree of cross-linking achievable."

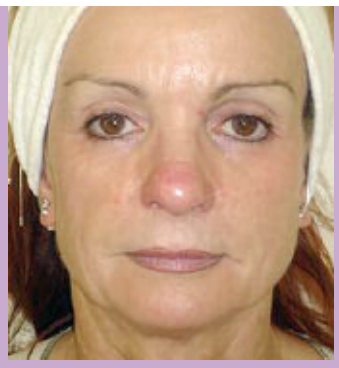
Cultured Human Fibroblasts

Isolagen, by Isolagen Corporation (Exton, Pa.), is a pioneering autologous cellular therapy, utilizing a patient's own fibroblast cells to stimulate collagen and elastin regeneration. The process starts with harvesting a 4 mm section of skin from behind the patient's ear, which is then shipped refrigerated to Isolagen Corporation, where millions of new healthy fibroblast cells are cultured under a patented process. Six to eight weeks later, the filler material is sent back to the physician, each vial containing 20 million cells. The fluid is then injected just under the epidermis into the desired area. This is repeated every two to four weeks for three sessions, with a potential touch-up treatment at four to six months. The cells gradually stimulate a network of collagen.

Optimal effects are seen between four and six months. Isolagen's cryogenic Cell Storage System allows a patient to permanently save these younger cells for use in years to come. This allows access, at any time, without having to go through another biopsy. This permits a patient to have fibroblast cells injected ten years from now that are actually ten years younger – a real injection of youth. The downside, in addition to the current unavailability in the U.S. (only available in the U.K.), is the time and cost – upwards of $1,000 per treatment session. Also, the shipping is complicated and the patient must show up for their injection or the cells die. Isolagen remains off the U.S. market while the company works to comply with FDA regulations. Currently in Phase III clinical trials here in the U.S., with a possible clearance in late 2006 or early 2007.



Before Tx



Full facial rejuvenation after only one Isolagen Tx

Other Collagens/Tissue

These products are obtained from cadaver tissue, much of it donated through tissue banks. Cadaver collagen is FDA regulated and must meet criteria established for extensive testing against infectious agents such as Hepatitis B,C, and HIV.

Fascian™, from Fascia Biosystems, LLC (Santa Monica, Calif.), is an injectable agent derived from cadaver human tissue known as the fascia lata, and is used primarily to treat skin defects such as depressed scars. The newer injectable form of Fascian is now being used for wrinkle therapy, and comes in several differently sized particles. Fascian is mixed with saline or lidocaine just before injection. Fascian takes several months to be reabsorbed and replaced by the patient's own tissue.

Hyaluronic Acid

The demand for hyaluronic acid (HA) is increasing rapidly and has fast become the gold standard for dermal enhancement. Global sales have progressed from $40 million in 2000 to over $300 million in 2005. This is primarily due to the ability of many HA products to meet the increasing patient demands for same day, non-animal, longer lasting options. Not all HA products are alike however, and many factors should be considered when choosing an HA filler. Specific aspects of an HA that should be looked at are; source of HA (avian or bacterial), concentration of HA, particle size, whether the HA is cross-linked, the type of cross-linking agent used, the amount of cross-linking agent used, viscosity, whether the HA is monophasic or biphasic, the inclusion of an anesthetic agent, type of syringe supplied, volume options, studies available of safety, stability, performance, etc.

The Restylane™ family of products, from Q-Med AB (Uppsala, Sweden) and Medicis Aesthetics (Scottsdale, Ariz.), is the protagonist in progressing the modern filler market. This groundbreaking substance, Non-Animal Stabilized Hyaluronic Acid

Restylane by Q-Med AB

(NASHA), is produced biotechnologically by bacterial fermentation (streptococci) and only minimally modified cross-linked (stabilized) with BDDE (1,4-butanediol diglycidyl ether).

Elizabeth Bergstedt, medical marketing manager for Q-Med (Uppsala, Sweden), explains the Restylane advantage over most HA products: "The NASHA gel is stabilized in a two-step process, preserving the integrity of the HA in its most natural and unaltered form (manipulated by less than 1% – using the least amount of cross linking agent and thus less risk of inflammation or reactions). As the NASHA gel dissipates, each Restylane molecule progressively binds more water (isovolaemic degradation) – the volume is maintained until the hyaluronic acid is almost fully degraded and disappears completely over time."

Currently Restylane is sold in over 75 countries and has reached a milestone of over four million syringes sold to date as of 2006. The clinical evidence with the Restylane portfolio is unsurpassed by any other HA company, as we have over ten years of controlled clinical trial data on these products.

The entire Q-Med hyaluronic line is based on its NASHA technology and is differentiated by concentration and size of the HA particles; Restylane™ – 100,000 particles per ml, is intended for the correction of superficial wrinkles. Restylane PERLANE™ – 10,000 particles per ml, is used for the filling out of deeper folds but also for the treatment of lips. Restylane TOUCH™ (Fine Lines) – 500,000 particles per ml, is used primarily for the correction of thin, finer wrinkles and lines. Restylane SUB-Q™ – 1,000 particles per ml, is intended for sculpting and forming the contours of the face, for example making the cheeks or chin more pronounced by providing increased volume in the facial tissue. Restylane LIPP™ is the latest innovation from Q-Med, launched in Europe in January 2006.

Anne Rhenman, Q-Med's director investor relations and corporate communications, explains, "Restylane LIPP is tissue-tailored and formulated to work in harmony with the natural anatomy of the lip. Based on patented NASHA technology, Restylane LIPP, which is biologically degradable, has a cohesive yet dynamic gel configuration and is structured to retain its shape, despite the complex movements and rich vasculature associated with the lip area." In the U.S., Medicis expects FDA approval for TOUCH and PERLANE in 2006. Also, they have launched Restylane Rewards to assure consistent patient participation. This program allows patients to earn up to $375 in rewards when they have treatments every six months, or sooner (up to a total of four). After each treatment they are rewarded with a gift card, as well as a bonus after the fourth treatment.

Puragen™ and Puragen Plus™, by Mentor Corporation (Santa Barbara, Calif.), is the first hyaluronic acid-based injectable to utilize a breakthrough technology called DXL™. This patented process double cross-links hyaluron molecules, providing greater resistance to degradation than single cross-linked hyaluronic acid fillers. Puragen is non-animal based, eliminating patient allergy concerns. Puragen is the latest hyaluronic acid product to be launched in Europe (May 2005 – approved as a CE-marked Class III intradermal implant for facial wrinkles and folds in Europe) and is expected to be authorized by the FDA for sale in the U.S. in early 2006.

Bruce Osborn, marketing manager, facial aesthetics for Mentor Corporation, describes the Puragen DXL technology advantage, "DXL technology (double cross-linked hyaluronic acid with 20 mg/g) is the result of a process that stabilizes extremely pure HA chains using a two-stage cross-linking process with two separate types of bonds. Only DXL uses 1,2,7,8-diepoxyoctane to create both ether and ester bonds. A slightly hydrophobic nature results, which increases the gel network physical bonding. Combined with the additional ester bonds, this molecular configuration greatly slows the degradation rate of the DXL network by reducing the diffusion rate of the enzyme hyaluronidase into the matrix (no other hyaluronic filler features both ether and ester bonds). Most importantly, small particle benefits are now complimented by large particle resilience, extending product duration in the body. Now, only one HA filler may be needed for all uses. Results should last a minimum of 6 to 12 months."

Puragen Plus with DXL technology will include lidocaine, and is to be launched in late 2006 / early 2007. Mr. Osborne continues, "Puragen Plus will be the only HA filler on the market which offers the advantage of built-in anesthetic. The DXL technology provides a level of HA stability allowing the incorporation of lidocaine – increasing patient comfort over other HA products. We wanted to bring back to the market a filler advantage patients enjoyed in the past but had to give up with HA products."

Hylaform/Hylaform Plus, developed by Genzyme Biosurgery (Cambridge, Mass.) and marketed by Inamed in the U.S. and select other countries, are highly purified avian sourced (rooster combs) cross-linked forms of hyaluronic acid [(Hylan-B) with sulfonyl-bis-ethyl cross-links between hydroxyl groups of the polysaccharide chains of hyaluronan]. Hylaform is indicated for injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and nasolabial folds. Hylaform Plus is formulated with a larger particle size, indicated for correction of deeper wrinkles and facial contouring. Results average five to six months. No skin test is required for either product. A good product, but the trend is to avoid animal sourced HA.

To circumvent the aversion to animal based HA's, Inamed has launched Captique – the newest dermal filler entry to the U.S. market based on Genzyme's proprietary non-animal stabilized hyaluronic acid technology and distributed by Inamed. Captique is an excellent cross-linked hyaluronic acid with a concentration of 5.5 mg/ml, indicated for the correction of moderate to severe facial wrinkles, with a solid performance of five to six months. Captique has not taken off like it could, mainly because Restylane has established itself so well in markets around the world.

Juvéderm™, manufactured by LEA Derm a subsidiary of Corneal Group (Paris, France), is a patented single phase cross-linked (BDDE – 1,4-butanediol diglycidyl ether) hyaluronic acid – phosphate buffered to 6.5 - 7.3 pH. Leslie Baumann, M.D., chief, division of cosmetic dermatology, associate professor, department of dermatology, University of Miami and author of *The Skin Type Solution* comments, "Juvéderm is an interesting new filler that offers ease of use, softness, and longevity when compared to other HA fillers. It uses cross-linking technology that gives it a long duration but does not make it feel stiff as some other HA products do. There are six types of Juvéderm so you have many choices within the Juvéderm family." Juvéderm 18 is the least cross-linked version, indicated for superficial indications. Juvéderm 24 is indicated for deeper wrinkles and defects. Juvéderm 30 is indicated for deeper furrows such as nasolabial folds. All do not require a skin test, are biocompatible, and have the highest concentration of hyaluronic acid of any filler available today (18 mg/g to 24 mg/g of HA) providing lasting results and greater direct volume to the skin.

William Philip Werschler, M.D. comments, "This is the best HA so far, providing a soft and natural feel in tissues. It is easy to work with and the flow is great. Results are five to seven or more months. Juvéderm is excellent in the lips as people want soft lips – collagen is not as soft as HA's." Juvéderm products are currently approved or registered in over 36 countries, including all major European markets. Inamed licensed the Juvéderm portfolio of HA products from the Corneal Group, securing exclusive rights to develop, market and distribute the products in the United States, Canada and Australia, and non-exclusive rights in France, Spain, the United Kingdom, Italy, Germany and Switzerland. Inamed began marketing Juvéderm in Canada in late 2005 and is expected to launch Juvéderm in the U.S. in 2006. In the non-exclusive European countries, Inamed will establish it as a new brand name – Hydrafill™ 1, 2 & 3, with sales beginning sometime in 2006.

Surgiderm®, by Corneal Group (Paris, France), is very similar to their Juvéderm HA portfolio. The patented single phase cross-linked hyaluronic acid formulations are available in four forms; Surgiderm 18 - 18 mg/g, Surgiderm 30 - 24 mg/g, Surgiderm 24XP - 24 mg/g, Surgiderm 30XP - 24 mg/g, and the newly launched Surgilips®. Surgiderm incorporates Corneal's new 3D Hyaluronic Acid Matrix Technology, which is said to allow for a tighter, more uniform, and greater number of cross-link structures – allowing greater resistance to degradation.

Teosyal by Teoxane

Teosyal®, by Teoxane Laboratories (Geneva, Switzerland) is a new range of monophasic non-animal based hyaluronic acid products with two formulas – Teosyal 27G and 30G - 25 mg/ml. Each are formulated with monophasic cross-linked hyaluronic acid macromolecules. According to Julien Delpech, director of Davai Group (Paris, France), the marketing group for Teoxane in 2005, "The primary characteristic is that the HA is formed as a strong cohesive gel ribbon and

Esthélis Basic, Soft and Men by Anteis SA

not as particles, providing high viscosity and elasticity and resistance to degradation and migration. Results will last six to nine months. Teosyal 27G is a very dense gel and is indicated for deep dermal layers. Teosyal 30G is more fluid and intended for superficial indications.

In 2004, Anteis SA (Geneva, Switzerland), launched its first range of products onto the aesthetic medicine market – Esthélis, and are now sold in 58 countries. Silvia Scherer, marketing director for Anteis describes Esthélis, "Our hyaluronic acid gels incorporate Cohesive Polydensified Matrix (CPM) technology – a polydensified monophasic cohesive gel material that is not formed into particles. CPM technology is based on a dynamic double cross-linking process of the cohesive monophasic HA gel with BDDE. The CPM process assures the cohesive HA gel is very fluid and easy to inject. Supplied in two different formulations, two volumes (0.6 ml and 1.0 ml), and as three clearly differentiated packages – Basic, Soft, and Men." In May 2005 Anteis SA entered a strategic partnership with Merz Pharmaceuticals (Frankfurt, Germany). Merz received exclusive license and marketing rights for Germany, Austria, Switzerland, Russia, and Italy to sell the Anteis portfolio under the name Belotero (Belotero Basic – Belotero Soft).

HylaNew and HylaNew Ultra, by Prollenium Medical Technologies, Inc. (Richmond Hill, Canada), are cross-linked non-animal hyaluronic acid gel products. HylaNew contains HA 25 mg and hypromellose 12.5 mg. HylaNew Ultra contains high viscosity cross-linked non-animal hyaluronic acid 25 mg and Hypromellose 15 mg. Results are seen for up to six months with HylaNew and nine months with HylaNew Ultra, with availability only in Canada – U.S. approval pending.

Semi-Permanent, Biodegradable

CaHA – Calcium Hydroxylapatite microspheres

BioForm's (San Mateo, Calif.) Radiesse® – 55.7% Calcium Hydroxylapatite (CaHA) 25-45 micron microspheres suspended in 36.6% water for injection USP, 6.4% Glycerin USP, and 1.3% Sodium Carboxymethylcellulose), is an excellent semi-permanent filler and has been used off-label for facial wrinkles, folds, and defects since 2001, with results seen for up to two years. CaHA is the major mineral component of bone and has been used for bone restoration for decades. It is highly biocompatible and no antigenicity testing is required. Dr. Werschler comments, "Radiesse is both stimulatory (40%) and replacement (60%). It is my favorite as far as feel to inject; with a wow factor that lasts up the 18 months." Clinical trials for FDA approval for nasolabial fold indications are under way, with an expectation of approval in 2006. The mechanism of action in Radiesse centers on the product being incorporated by the surrounding tissue and then being replaced by it (collagenisis) – broken down by hydrolytic enzymes into calcium and phosphate. It should be noted, use in lip augmentation is routinely discouraged now due to reports of potential lump formation."

DEAE Sephadex particles (Dextran)

MATRIDEX®, by BioPolymer GmbH & Co. KG (Siershahn, Germany), is a biodegradable gel containing cross-linked DEAE Sephadex dextran microspheres of 80-120 microns, with a positively charged surface. It works by stimulating new collagen (regeneration) via positively charged DEAE Sephadex microspheres.

HylaDex, by Prollenium Medical Technologies, Inc. (Richmond Hill, Canada), is comprised of cross-linked non-animal hyaluronic acid, 25 mg, Hypromellose 15 mg, and Dextronomer DEAE 25 mg. Intermediate volume is sustained by facilitating the skins ability to produce collagen and elastin. Results are seen for up to 12 months and available only in Canada, with U.S. approval pending.

PLLA – Poly-L-lactic Acid Microspheres

After a successful launch in Europe, New-Fill® was acquired by Sanofi-Aventis (Dermik, Berwyn, Pa.) and launched in the U.S. market in 2004 under the name Sculptra®. Sculptra has FDA approval for HIV-induced facial lipodystrophy, with all other applications in the U.S. being performed off-label. Dr. Werschler describes Sculptra, "Polylactic acid (PLLA), is a biodegradable synthesized corn material, which has been used safely for

decades as surgical sutures (Vicryl, Dextran), resorbable craniofacial plates and screws. Sculptra/ New-Fill is supplied in a dry powder form and is suspended with 5 ml water shortly before use (some use lidocaine as the suspension). Injections are reserved for the deep dermis, subcutis plane, since lumps or granulomas can develop. The mechanism of action is a pure foreign body reaction – stimulating neocollagenesis, resulting in a 3-D volume expansion and increased collagen production."

Dr. Narins comments, "Sculptra provides very good results, is excellent for adding volume, and is better when used in conjunction with other fillers and/or topicals. There are drawbacks however – it is expensive, time consuming, several treatments are needed, and is very technique dependent. Hence, Sculptra should only be injected by a physician."

Dr. Werschler explains his treatment protocols, "two to three treatments over a period of six or more weeks, with results plateauing after three to five treatments. The average patient cost is $2,000-$3,000. Touch-up treatments are sometimes needed at 6 to 12 months, with results lasting up to two years. It is impossible to inject too deeply within the skin but caution is needed not to inject too superficially. The first treatment should be injected diffusely to initially provide restoration and reserve the second treatment for enhancement objectives."

Permanent, Non-Biodegradable

PMMA – Polymethylmethacrylate Microspheres

ArteFill®, by Artes Medical (San Diego, Calif.), is a precision filtered dermal injectable with smooth round polymethylmethacrylate (PMMA) microspheres (20% by volume – 30 to 50 microns in diameter) suspended in purified U.S. bovine collagen gel (80% by volume – derived from calf hides obtained from a controlled, U.S. herd), and 0.3% lidocaine. Pending FDA approval for cGMP manufacturing at its dedicated manufacturing facility, Artes Medical anticipates final FDA approval of ArteFill in early 2006. William von Brendel, vice president of worldwide sales and marketing for Artes Medical, Inc., explains, "ArteFill will become the first FDA approved permanent micro-injectable treatment for nasolabial folds."

Artes Medical holds U.S. and international patents to protect its unique permanent micro-injectable technology coined, Aesthetic Tissue MicroGenesis™. This technology was originally developed by Gottfried Lemperle, M.D., Ph.D., former head of the department of plastic surgery and professor at the University of Frankfurt/Main, Germany, and sold under the Arteplast® and Artecoll® brand names by third party distributors.

ArteFill® is an advanced, third generation product developed by Artes Medical with less than 1 small PMMA particle below 20 microns among 100 microspheres of 30 to 50 microns in diameter. The ArteFill microspheres are biocompatible and safe, remain stable at the implantation site and are not removed by phagocytosis, retain volume and remain pliable, do not cause protrusion of the skin or mucosa, and induce only minimal foreign body reaction.

Aesthetic Tissue MicroGenesis™ involves the stimulation of the natural production of human collagen around each of the injected PMMA microspheres (acts as a scaffold), as the bovine collagen gel is being absorbed over three to six weeks. Aesthetic results are visible immediately and continue to improve during the tissue remodeling period. 80% of the final tissue augmentation consists of the patient's own collagen. Dr. Narins comments, "There is a tremendous desire for a safe and permanent FDA approved filler in the marketplace – one that can lift, fill and sculpt the face evenly over a few sessions. This will be the first permanent micro-injectable to be given FDA approval and I would expect both physicians and patients to be excited about this new treatment option. Since this is a permanent filler, training is important and it should only be injected by physicians with demonstrated expertise."

Injection fatigue is a term coined by the *Wall Street Journal* (October 2005), where patients who attain excellent temporary results with fillers end up wanting these results to last longer and longer, and ultimately drop out when they realize how often they need to return to maintain the desired enhancement level. According to Mr. von Brendel, "based on our market analysis, we believe three out of four dermal filler patients and three out of five Botox patients drop out eventually due to cost, pain, inconvenience and simple injection fatigue.

We believe ArteFill will fill the gap and provide physicians and patients a dermal filler option that provides a truly long lasting correction. We have developed a physician education and support system to help enable physicians to improve patient outcomes and satisfaction. All physicians will be accredited prior to being able to provide the product to help ensure the best clinical outcomes with this new category of aesthetic injectable. Note, the product has not been evaluated for lip augmentation.

PAAG – Polyacrylamide Gel

Aquamid® and Aquamid® Reconstruction injectable implants, by Contura International A/S (Soeborg, Denmark), are composed of 97.5% apyrogenic water bound to 2.5% cross-linked polyacrylamide. Aquamid® is non-resorbable, non-allergenic, biocompatible, migration resistant, immunologically inactive, and highly elastic. Aquamid® is indicated for lip augmentation and contouring minor facial folds. Aquamid® Reconstruction is made with higher viscosity, making it particularly well suited for deep folds and large depressions.

PAAG – Poly (acrylamide-co-DADMA) Gel

Outline™ and Evolution™, by ProCytech SA (Bordeaux, France), are absorbable Poly (acrylamide-co-DADMA) gels. The company explains, "poly(acrylamide-co-DADMA) has been used in medicine and the food industry for many years, for lens implants, artificial tears, contact lenses and water and wine purification. Outline replaces lost volume and provides the framework for new collagen formation via biodegradable spheres. Evolution is made from non-biodegradable spheres, about 40 microns in diameter, providing the initial and permanent volume augmentation.

Silicone (LIS)

Silikon 1000®, by Alcon Labs (Fort Worth, Texas), was FDA approved for retinal detachments in 1997, and Silskin®, by Richard-James, Inc. (Peabody, Mass.), received an Investigational Device Exemption (IDE) for a clinical trial on facial wrinkles in 2003. Both products are used off-label as permanent facial fillers. Typical protocols involve three treatment sessions with fees averaging around $1,500, with physician costs of $100 per 8 cc vial.

The introduction of the microdroplet technique has led to a revival of purified silicone gels and their off-label use as a facial filler. Millions of nano-droplets are formed after serial puncture injections of small quantities of silicone. Silicone as nano-droplets, being so biocompatible, a foreign body response is not stimulated in most cases, and past complications of migration and granuloma formation are reduced. Dr. Narins stresses, "Physicians must use the microdroplet technique over multiple treatments. One should never use more than 0.5 cc per treatment. It is important not to inject into the wrong level or use wrong volume – it must be used slowly. Being a permanent filler, it is imperative that silicone be limited to physicians use only. What is needed is a big company to come in to perform the proper safety and substantiation studies and provide the in-depth level of training and support required."

Debut of Prollenium Fillers

Prollenium Medical Technologies (Richmond, Ontario, Canada), has recently unveiled their newest innovation in dermal filling. The HylaNew product line is made up of three clear, non-animal, hyaluronic acid (HA) gel fillers featuring the highest concentration of cross-linked HA available. In addition to the 25 mg of cross-linked HA, each of the three fillers also contain 25 mg of non cross-linked HA, which hydrates the injection site and surrounding tissue, replenishing HA that is lost to aging. The HylaNew product line also incorporates Hypromellose (an eye lubricant) which makes the gel easy to inject and causes less bruising and swelling for the patient.

HylaNew, a biodegradable clear cross-linked HA gel filler. HylaNew is best used to fill superficial imperfections in the dermis such as fine lines, forehead wrinkles, crow's feet, perioral lines and small folds and lines.

HylaNew Ultra, a high viscosity biodegradable clear cross-linked HA gel filler is a longer lasting filler used for smoothing out deeper wrinkles and folds. The increased concentration of Hypromellose and the use of high viscosity HA makes HylaNew Ultra especially ideal for lip augmentation.

HylaDex is the longest lasting of the three fillers (with an implant life of up to 24 months). HylaDex is a biodegradable clear, cross-linked HA gel filler with Dextranomer beads. These positively charged beads stimulate the formation of soft tissue. HylaDex is indicated for medium to deep sized wrinkles and folds and is ideal for chin/cheek augmentation.

The HylaNew product line has been designed to improve upon the most common deficiencies in HA fillers. Longer, more stable implant life is achieved through 25 mg of cross-linked HA, the highest concentration available. Traditional fillers are also very hydrophilic, drawing in moisture from surrounding tissue. While this is beneficial to the implant, it is detrimental to surrounding tissue. HylaNew, HylaNew Ultra, and HylaDex have addressed this problem by including 25 mg of non cross-linked HA in each syringe. This not only hydrates the surrounding tissue, but also replenishes HA lost to aging rejuvenating the skin.

Positively charged Dextranomer beads found exclusively in HylaDex, attract the body's own collagen and elastin (soft tissue) to the injection site. This results in dermal filling through cross-linked HA and collagen regeneration. ■