New Fillers under Consideration: What Is the Future of Injectable Aesthetics?

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ABSTRACT

The past 5 years in the United States have seen an explosion in the popularity of noninvasive aesthetic procedures. Not only have fillers and Botox turned out to be fantastically reliable and effective aesthetic tools, but also they have vastly expanded the accessibility of cosmetic procedures. Our cosmetic filler options are growing quickly as more and more fillers are coming before the U.S. Food and Drug Administration (FDA), seeking entry into the lucrative U.S. market. This article outlines the approval process that foreign fillers go through in their home countries and gives an idea of the fillers that are currently under consideration by the FDA. As our armamentarium of injectable fillers grows, it will be essential to know each product's strengths and weaknesses so that we can provide our patients with the best possible aesthetic results.

KEYWORDS: Injectable, filler, medical device, FDA, CE mark, hyaluronic acid, collagen, polyacrylamide, Aquamid, Atlèan, Novielle, Voluma, Juvéderm, Evolence, Prevelle, Belotero, Varioderm, Amalian, Teosyal

The past 5 years in the United States have seen an explosion in the popularity of noninvasive aesthetic procedures. Physicians are turning more and more toward botulinum toxin type A (Botox Cosmetic, Allergan Inc., Irvine, CA) and the recently U.S. Food and Drug Administration (FDA)-approved injectable fillers as patients are demanding inexpensive, risk-free, and natural-looking cosmetic enhancement. Not only have fillers and Botox turned out to be fantastically reliable and effective aesthetic tools, but also they have vastly expanded the accessibility of cosmetic procedures. Aesthetic refinement is no longer the exclusive province of the wealthy. Even Joe the Plumber can get a little Botox to soften his glabellar lines.

Aesthetic procedures became increasingly mainstream at the same time as the Internet vastly expanded the average consumer's access to information that was heretofore exclusive to physicians. The result has been an explosion of patient demand for these procedures. Much of the innovation in nonsurgical or filler-based procedures is rapidly disseminated by Internet-educated patients who push their local physicians to keep up with developments from around the world.

Because of the lengthy approval process of the FDA for medical devices, the United States has relatively few injectable fillers available on the market. Most other countries have several times the number of fillers to choose from. Unfortunately, this increased choice does not always translate to better treatment, as some of these fillers are of dubious quality. Overall, American patients have benefited from the relative laxity of worldwide regulatory agencies. By the time a cosmetic filler is up for FDA consideration, there is usually a wealth of European and Asian data on its safety and efficacy.

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Interpreting the international data sometimes poses challenges, however. Some countries have a hard time enforcing standards of who can or cannot inject aesthetic fillers. Problems can occur when these fillers fall into the wrong hands. When evaluating adverse effects data, attention must be paid to whether the injection procedure was performed in a dermatologist's office or at the neighborhood hairdresser shop.

So how are medical devices like injectable fillers certified for use outside of the United States?

The certification process that results in approval of an injectable filler for use in the European Union and Great Britain is governed by the Medical Device Directive. This set of rules is different in the United Kingdom and Europe compared with the rules for certification United States. One of the major differences is that prospective human trials are not mandatory for the approval of an injectable filler in the European Union and the United Kingdom as they are in the United States. The European regulatory bodies (called notified bodies) will consider a combination of retrospective human trials and preclinical animal biocompatibility studies sufficient to indicate safety in the majority of cases. Filler substances that are well established in the scientific literature will usually obtain a CE marking (Conformité Européene—certifying that a product has met the health, safety, and environmental requirements of the European Union) with this kind of information. The other class of information required for approval is documentation that the manufacturing process of the filler follows all International Organization for Standardization (ISO) standards. Materials that are not very well studied have to go through more rigorous human trials prior to receipt of a CE mark. Regulations vary, however, by the country involved and are not standard throughout the European Union.

The process starts with an application for approval that is submitted by the manufacturer of an injectable filler to their country's "Competent Authority." The Competent Authority is an institution that is set up by the governmental health ministry or medical agency. It is similar to the FDA in that it approves the study protocols and certifies the use of pharmaceuticals. The Competent Authority does not, however, approve medical devices like injectable fillers for use. That function is reserved for nongovernmental organizations called "Notified Bodies." These are private organizations that are certified by the government to examine the data generated by the approved protocols and perform safety, quality, and performance review testing. The Notified Bodies grant the CE mark that is required to market an injectable filler.[1]

Within the Medical Device Directive, there are four categories of devices, stratified by potential risk posed to the patient. The least invasive of these, such as external patient support devices, are classified as category I. More invasive, but not indwelling, devices, such as catheters, are classified as category IIa. Inactive indwelling implants, such as injectable fillers, are classified as category IIb. The last category, category III, is reserved for active implants, such as pacemakers. The approval process varies in complexity according to the category.

Once a filler gets a CE mark in a European country or the United Kingdom, it can be marketed throughout Europe, Australia, and the United Kingdom. Some countries in Asia accept the CE mark, such as Singapore. Others, like China and Japan, require clinical studies performed locally. Injectable fillers are only sold to physicians, in most cases, and doctors are usually the ones doing the injecting. Most countries do, however, permit the physician to delegate filler injections to nurses, but not to estheticians or medical assistants.

Medical device approval in the Russian Federation is a somewhat Byzantine endeavor with few published guidelines. The Federal Service for Control over Healthcare and Social Development (Roszdravnadzor) is the main government agency responsible for registration of medical equipment. Russian-made medical devices are inspected, studied, and certified by this agency. Foreign companies that want to market injectable fillers within Russia must partner with a Russian corporation, a Russian distributor, or a Russian consultant company that guides them through the approval process. Because the testing, certification, and adverse event reporting process is somewhat opaque, it is difficult to judge the safety of Russian-made medical devices at this time.

Latin American regulations vary by the country. Unfortunately, enforcement of those regulations varies as well. The countries with the longest record of enforced regulations include Brazil, Argentina, and Mexico. Countries like Uruguay, Colombia, Peru, Ecuador, Guatemala, and Venezuela have regulatory processes, but these are suboptimally enforced.

The following is a partial list of cosmetic fillers that are being considered for approval by the FDA.

Aquamid: A long-lasting (more than 5 years), biocompatible hydrogel made of 97.5% sterile water and 2.5% cross-linked polyacrylamide. It incorporates into the tissues without a significant inflammatory response, so its filling effect is, more than most fillers, due to its injected volume. Large European case studies show relatively minimal adverse effects. Manufactured by Contura in Denmark.

Bio-Alcamid: A long-lasting 4% polyalkylimide hydrogel. This filler has been used in large quantities for facial lipodystrophy as well as breast, buttock, and calf

augmentation.[2] A capsule of biofilm forms around the "endoprosthesis,"[3] limiting its interaction with the immune system. It was said that this made the material more biocompatible, but this capsule is now considered one reason why the material is prone to abscess formation and migration.[4] Manufactured by Polymekon in Italy.

Novielle: A polymer gel product currently in use for vocal fold medialization. The Novielle Gel version lasts for 9 to 12 months and the Novielle GelPlus version lasts for up to 24 months. Manufactured by Coapt Systems in Palo Alto, CA.

Voluma: A non-animal hyaluronic acid (NAHA) gel injected into the subdermis specifically for volumization.[5] Voluma NAHA is cross-linked with 1,4-butanediol diglycidyl ether (BDDE)—the standard cross-linking agent for both Restylane and Juvéderm. Voluma contains a mixture of high- and low-molecular-weight NAHA, with a concentration of 20 mg/mL. Although there is not much clinical data, Voluma seems to cause few adverse events, and duration of effect is between 6 and 18 months. Manufactured by Allergan (Irvine, CA).

Juvéderm with Lidocaine: 0.3% lidocaine is added to the NAHA to improve patient comfort during injection.[6] This formulation is in widespread use throughout Europe and the United Kingdom in a range of several products with variable density and amount of cross-linking. The lidocaine does not seem to affect the rheology or duration of effect of the Juvéderm. Frequency of adverse events also seems to be unaffected. Manufactured by Allergan.

Evolence Breeze: A smoother flowing version of the recently FDA approved (35 mg/mL porcine collagen in phosphate-buffered saline) Evolence product. Like the rest of the Evolence family, Evolence Breeze is biocompatible (no allergy testing required), cross-linked with ribose, and lasts ~12 months. Evolence Breeze is designed for use mainly in lips and fine lines. Manufactured by ColBar Life Science Ltd, Herzliya, Israel. Distributed by Johnson and Johnson, Langhome, PA.

Prevelle Shape and Prevelle Volume: These are variants of the currently FDA-approved NAHA filler Prevelle Silk. Prevelle Silk was the first FDA-approved filler to contain lidocaine. However, it has a lower hyaluronic acid (HA) concentration (5.5 mg/mL) than that of other HA fillers and suffers from a relatively shorter duration of effect. These formulations are designed to increase duration of effect by increasing cross-linking, HA concentration, and particle size. Manufactured by Mentor (Santa Barbara, CA).

Belotero: Monophasic, double cross-linked NAHA. The Belotero Basic version has 22.5 mg/mL NAHA. It is injected into the deeper dermis with a 27-gauge needle and is used for volume replacement and deeper lines. The Belotero Soft version has 20 mg/mL NAHA. It is injected into the upper dermis with a 30-gauge needle and is used for fine lines and lip enhancement. Duration of effect is in the 6- to 9-month range. The company claims that its manufacturing process gives Belotero a uniquely soft cosmetic effect. Manufactured by Anteis in Switzerland and distributed by Mertz.

Varioderm: A family of cross-linked NAHA fillers. Varioderm Fine Line: 6 mg/mL HA for upper dermis injection. Varioderm: 12 mg/mL HA for mid-dermis injection. Varioderm Plus: 18 mg/mL HA for deep dermis injection. Varioderm Subdermal: 27 mg/mL HA for contouring and volumizing injections at the subdermal level. Duration of effect is 6 to 16 months, depending on the variant being used. Manufactured by Adoderm GmbH, Germany.

Amalian: Another family of NAHA products where HA concentration varies with function. The Amalian I product (8.4 mg/mL) is designed for superficial injection, whereas the Amalian II and Amalian III products are designed for deeper lines and volumization. Amalian is a combination of monophasic and biphasic HA gels. Microparticles of cross-linked HA are dispersed in lonzg chains of non–cross-linked HA. The company claims that this formulation increases duration of effect. Clinical data are still sparse. Manufactured by Nordic Aesthetics in Sweden.

Teosyal: A 25 mg/mL monophasic NAHA product that claims to have less proteins and bacterial endotoxins than other NAHA fillers, making it less likely to cause irritation and complications. Teosyal is made in a variety of densities and particle sizes for lip augmentation, filling wrinkles, and volumization. Duration of effect varies from 6 to 12 months, increasing with density and particle size. Manufactured by Teoxane in Switzerland.

Atlèan: A collagen stimulating volumizer agent designed to compete with Sculptra. A 1-mL syringe contains 70 mg tri-calcium phosphate (TCP) and 18 mg NAHA in 1 mL buffered saline solution. The TCP stimulates long-term collagen production, and the NAHA provides immediate cosmetic results so that the patient does not have to wait several months to see the effect (like with Sculptra). Duration of results is ~12 months, according to the manufacturer. Manufactured by ABR Development in France.

Outline, Matridur, Laresse, Puragen, Hydrafill, Surgiderm, DermaLive, and DermaDeep are all fillers that are having problems in Europe and have been withdrawn from the market in the United Kingdom. The troubles are mostly linked to unacceptably high frequencies of serious adverse events.

Injectable filler–based procedures are popular, but we are nowhere near the crest of this wave. A new crop of products is poised to provide aesthetic physicians with better, safer, and cheaper options to satisfy the public's growing demand for affordable, low-risk, natural-looking cosmetic enhancements. The FDA is responding to the expansion in the field of injectable fillers by improving the mechanism of safety testing, adverse event reporting, and product labeling. Innovative doctors are forging the future of aesthetic medicine as they discover better ways to accomplish traditional aesthetic goals. They are also using these new tools to set new goals and raise the expectations for our field. As our armamentarium of injectable fillers grows, it will be essential to know each product's strengths and weaknesses so that we can provide our patients with the best possible aesthetic results. The future is bright indeed, as long as we maintain our good judgment and always advance our patient's best interests.

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