6 FILLERS IN EUROPE

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KEY POINTS

(1) Many more fillers are available in Europe as compared to the USA
(2) Fillers in Europe can be divided into those that are short-acting, intermediate-acting and permanent
(3) In general, the regulatory process for fillers in many parts of Europe, is not as stringent as that seen in the USA
(4) Permanent fillers can create long-lasting or permanent complications

INTRODUCTION

In the early 1990s, after a long period of bovine collagen use, hyaluronic acids (HAs) became the most commonly used biodegradable fillers in Europe in both dermatology and plastic surgery. Currently, HAs are very popular for both soft tissue augmentation and facial volume restoration.

Dermal filler HAs, as discussed elsewhere in this book, have a high water retention capacity and are both effective tissue volume correctors and well tolerated. Initially, HAs were extracted from rooster combs. Later, techniques were developed to produce HAs by bacterial fermentation. Currently, some of the newer HAs are formed with crosslinking to increase their longevity once injected into human skin.

In addition to the very popular HAs, other European fillers (some of which are not available in the USA) are either non-degradable or slowly degradable. They have now been used for 30 years for the correction of facial volume wasting.

Since some commercially produced HAs and non-degradable fillers can contain residues from the manufacturing process, it is important to understand the latter for each filler. Although two fillers may both be based on HAs, they are not necessarily the same. With the wide availability of so many dermal fillers and the minimal requirements for placing such fillers in the market-place, European physicians must often be concerned about follow-up studies over the short, mid, and long term.

In Europe, CE marking is obligatory before a manufacturer can market a filler product. However, the presence of a CE mark does not necessarily mean that the product's efficacy and side effects have been subject to any objective

clinical studies. The European approval procedure, which is much less rigorous than that in the USA, is expected to change soon, with the adoption of an approach similar to that used by the US Food and Drug Administration (FDA). It is hoped that soon European approval will be granted only after strict clinical studies critically evaluating both efficacy and safety.

This chapter explores most of the products currently utilized in Europe as of 2006. These fillers are of animal, bacterial or synthetic origin; they may be reticulated or non-reticulated. They are used to restore lines, increase volume or as filler product vectors.

Before one attempts to use any of the many available products, it is essential to have a thorough understanding of their absolute and relative contraindications, the types of anesthesia required, the differences between the types of wrinkles treated, and the techniques utilized to optimize cosmetic results.

Any injected product may have side effects, the severity and the outcome of which depend on the nature of the product used. Biodegradable products generally have milder, shorter-lasting side effects.

In general, allergic reactions are found to occur in 1–3% of patients. With some fillers, a preliminarily double allergy test is justified. It is also advisable not to inject biodegradable fillers in a site previously injected with a non-degradable product. Unfortunately, precise statistics, centralized data, results, and side effects are not available for many currently utilized fillers. This information can only be obtained from double-blinded randomized studies. These data are not only necessary for the safety of patients, but also required to improve physician knowledge and understanding of available products.

Of all the filler agents available in Europe, HAs are the most commonly used. Despite the fact that many questions still remain unanswered, these short-acting fillers do produce very significant results. The other available non-absorbable and/or slowly absorbable fillers, although highly efficient, can be associated with significant (albeit rare) complications. The ultimate goal in Europe is for higher approval standards than the currently used CE mark. Both patients and physicians will be helped when the current filler standards in Europe are brought up to the level of the French Approval for Marketing Medications (AMM) and the US FDA.

LEGAL ASPECTS OF DERMAL FILLER USE IN EUROPE

HA products in Europe, as in the USA, are classified as medical devices rather than drugs (botulinum toxins, however, are considered to be drugs) (Table 6.1).[1,2] These fillers, like all medical devices in Europe, are classified according to their perceived risk into classes I, IIa, IIb, and III (Table 6.2) on the basis of 18 rules (Table 6.3). Class I devices are considered to be the least dangerous and Class III the most dangerous.

Injectable biodegradable fillers are considered to be class III devices, whereas non-biodegradable products are (somewhat paradoxically) con-

Table 6.1 Definitions of drugs and medical devices from the French Ministry of Health

Drug definition	*Medical device definition*
• Any substance or product presented as having curative or preventive properties with regard to human or animal diseases • Any product that can be used in humans or animals in order to establish a medical diagnosis or to restore, change or modify their organic functions • Any ingested product that contains in its composition a chemical or biologic substance with no food value, but used for medical testing • Products used for disinfecting dental prostheses, and those intended for home use, are *not* regarded as drugs	• Any instrument, apparatus, equipment, material, product (except products of human origin), or article used alone or in association with accessories and software that is intended by the manufacturer to be used in humans for medical purposes, where the desired principal action is not obtained by pharmacologic, immunologic, or metabolic means, but whose function can be assisted by such means • Medical devices that are designed to be implanted totally or partly in the human body or are placed in natural orifices, and/or which depend for their function on an electrical source of energy or any source of energy other than that generated directly by the human body or gravity, are considered active implanted medical devices

Table 6.2 Definition of risk classes for medical devices from the French Ministry of Health

Class	*Class definition*
I	Week potential risk: surgical instruments, non-invasive medical devices, and invasive medical devices for temporary use
IIa	Moderate potential risk: medical devices that are sterile, contact lenses, dental prostheses; invasive medical devices intended for short-term use, invasive surgical devices
IIb	High potential risk: medical devices intended for long-term implantation
III	Critical potential risk: medical intended for long-term implantation in contact with the heart, central circulatory system or central nervous system; implanted degradable medical devices and/or breast implants

sidered to be class IIb, i.e. less dangerous devices. If, however, a non-degradable substance is combined with a degradable substance (with the non-degradable substance being considered to be a vector), then the filler device is considered to be of class III.

Regulation of filler products, as medical devices, is according to European Directive 93/42/CEE (14 June 1994). This regulation has been incorporated into French law 94-43 of 18 January 1994 as part of the laws of public health and social protection.[3]

Whereas medical drugs in Europe, much as in the USA, are subject to extensive, lengthy, and costly studies, medical devices in Europe can be marketed after CE approval is obtained – a fairly simple, less expensive approach. The CE marking simply attests to 'the conformity of the product to the essential requirements of an obligatory level of health security'. These standards (NF ISO13485, which are an adaptation of DM standard ISO 90001) (Table 6.4),

Table 6.3 Rules upon which the risk classification of medical devices is based from the French Ministry of Health. The classification is determined by the characteristics or combination of characteristics in connection with the actual use of the device. The ultimate classification corresponds to the highest rule associated with that device

1	Devices that have no contact with the patient or that come into contact only with intact skin
2	Devices stored for later administration
3	Devices capable of modifying the biologic or chemical composition of blood or other body fluids
4	Devices coming into contact with injured skin
5	Devices that are invasive and introduced through any bodily orifice
6	Devices that are invasive and of a surgical type intended for temporary use
7	Devices that are invasive and of a surgical type intended for short-term use
8	Devices that are invasive and implanted for long-term use
9	Devices that are therapeutic and intended to provide or to exchange energy
10	Devices of diagnostic use
11	Devices that are active and intended to manage or to withdraw drugs or other substances from the body
12	All other active devices
13	Devices containing medical substances
14	Devices used for contraception or for the prevention of sexually transmitted diseases
15	Devices intended specifically to disinfect, clean, or rinse
16	Devices that are inactive and are intended to record images
17	Devices of animal or derivative origin
18	Devices containing blood

Table 6.4 The ISO (International Standards Organization) standards

ISO 9000 standard is used as a guide for a group of four standards:

- *ISO 9001:* Quality system, models of guarantee of quality in design, development, production, installation, and associated services
- *ISO 9002:* Quality system, models of guarantee of quality in production, installation, and associated services
- *ISO 9003:* Quality system, models of guarantee of quality for final control
- *ISO 9004:* Management of quality and elements of the quality system

The standard medical NF ISO 13485 related to devices is an adaptation of the general standard ISO 9001. It lays down requirements to be respected by manufacturers of medical devices to satisfy the requirements of international law regarding management of quality and the provision of an effective and secure device

simply attest to quality assurance regarding the design, development, and production of the product, and to quality assurance regarding the installation and/or the associated services (such as the promotion of the product).

The rules for obtaining a CE marking are uniform throughout the entire EU. These rules require the following:

(1) The manufacturer must classify a device, as described above, according to the 18 rules of European Directive 93/42/CE into one of the four classes I, IIa, IIb, or III. In addition (at least in France), a request must be made to the AFSSAPS (French Agency for Medical Security of Health

Products) for the declaration of the product as a medical device (for class IIb and III devices).

(2) The manufacturer must maintain a file that tracks the manufacturing quality of a medical device according to NF ISO 13485. Such records document a description of the manufacturing process (including biocompatibility), the results of the validation of the manufacturing process (especially for sterilization), a list of raw materials utilized, a specification of these materials and a list of their components, and a final documentation of the product (labeling and instructions).

(3) The manufacturer must establish the conformity of the product with the essential requirements of European Directive 93/42/CE, in particular with regard to biocompatibility (conformity with the international standard ISO 10993-1 and with clinical data).

Indeed, it is the obligation of the device manufacturer to present clinical data on both the efficacy and side effects of the medical device. However, these data can only be data from the relevant scientific literature. An evaluation of effectiveness and side effects based on prospective clinical trials must be presented before any group III medical devices (such as HA acid fillers) can be used.

Ultimately, the situation is that marketing a dermal filler in Europe is constrained more by manufacturing standards than by safety and efficacy standards – which are minimal. The rules are much less stringent than for the development and marketing of a medical drug.[4] Finally, it should be noted that the assignation of a CE marking is only temporary – often for 3 years. This emphasizes the need for more long-term vigilance about these medical materials by the physicians that use them. This policy of vigilance is not a uniform directive throughout Europe.[5] In France, long-term scrutiny of medical devices is assured by AFSSAPS. This agency obliges the manufacturer, users (including expert noting any complications), or others who have been informed of an incident or a risk of incident that involves either directly or indirectly the death or serious damage to the health of a patient or a user to declare this incident to AFSSAPS. If this rule is violated, the offender risks a 4-year prison sentence and a 75 000 Euro fine.[6] However, it is only optional for the manufacturer, users, and others, having been informed of a complication and/or non-desired reaction, to report this problem.[4,7]

In conclusion, marketing of a filler in Europe requires only that a CE mark be obtained – which is a much less stringent requirement than FDA approval. Obtaining a CE mark in no way implies that a particular product was submitted to any clinical trials or any study of its effectiveness and possible short-term or long-term side effects. The law simply requires (at least in France) that professionals (doctors and manufacturers) declare to AFSSAPS any serious side effects and 'strongly advises them' to report other less serious side effects noted after using these products.

BIODEGRADABLE ABSORBABLE PRODUCTS AVAILABLE IN EUROPE

A wide range of absorbable products are currently available in Europe (Tables 6.5 and 6.6).[8]

It should be noted that collagen products from the USA (Cosmoderm/Cosmoplast; Inamed), described in Chapter 2 of this book, as well as the Israeli collagen product Evolence (Colbar Laboratories) are not described in this chapter.

Linked Hyaluronic Acids of Animal Origin

Hylaform

Hylaform (Genzyme; distributed in France by Inamed Aesthetic) received its CE mark in 1995 and FDA approval in 2004. Hylaform products are HA extracted from rooster combs. Although the manufacturer at one time suggested that the product is free from any associated proteins, the medical literature suggests that there may be some traces of potentially antigenic residue.[8] In Europe, the material is currently marketed in three forms:

- Hylaform Fine Line is slightly crosslinked HA, in a 0.55 ml syringe with a 32-gauge, ½-inch needle
- Hylaform is more strongly crosslinked HA, in a 0.55 ml syringe with a 30-gauge, ½-inch needle
- Hylaform Plus is even more strongly crosslinked HA, in a 0.55 ml syringe with a 27-gauge needle

Linked Hyaluronic Acids of Non-Animal Origin

These products are manufactured by bacterial fermentation.

Beauty Gel

Beauty Gel (Rofil Medical International, Germany, distributed in France by Philoderm) has received its CE mark but does not have FDA approval. This material is marketed in two forms:

- Beauty Gel is crosslinked HA, in three 1 ml syringes with 30-gauge, ½-inch needles
- Beauty Sphere is HA together with dextran

Dethail

Dethail (Phitogen, Italy; distributed in France by Phitogen France) received its CE mark in 2005 but does not have FDA approval. This HA is dextran-associated. The material is marketed in two forms:

Table 6.5 Hyaluronic acid (HA) products

Biorevitalization: non-linked HA	*Implants: linked HA*	*Vectors: slowly linked HA*
Animal origin		
Achyal	Hylaform:	
Ial System	Hylaform Fine Line	
	Hylaform	
	Hylaform Plus	
Bacterial fermentation origin		
Hyaluderm	Beauty Gel:	
Juvelift	Beauty Gel	
Mac Dermol:	Beauty Sphere (HA + dextrans)	
Mac Dermol Bio	Dethail (HA + dextran):	DermaLive (HA + acrylic hydrogel)
Mac Dermol S	Dethail Coilingel	
Restylane Touch Line	Dethail Lastingel	
Revitacare	Esthelis:	
	Esthelis Basic	
	Esthelis Men	
	Esthelis Soft	
	Hyaluderm:	
	Hyaluderm	DermaDeep (HA + acrylic hydrogel)
	Hydra Fill:	
	Hydra Fill 1	
	Hydra Fill 2	
	Hydra Fill 3	
	Juvéderm:	
	Juvéderm 18	
	Juvéderm 24	
	Juvéderm 30	
	Juvéderme 24HV	
	Juvéderme 30HV	
	Mac Dermol:	
	Mac Dermol R	
	Matridur:	
	Matridur	
	Matridex (HA + dextrans)	
	Puragen:	
	Puragen	
	Restylane:	
	Restylane Fine Line	
	Restylane	
	Perlane	
	Restylane Sub-Q	
	Rofilan Gel:	
	Rofilan Hylan Gel	
	Reviderm Intra (HA + dextrans)	
	Surgiderm:	
	Surgiderm	
	Voluma	
	Voluma	

Table 6.6 Linked hyaluronic acid (HA) products

Product (CE marking/FDA approval)	*Origin*	*Syringe*	*Needle*
Hylaform (1995/yes, 2004):			
Hylaform Fine Line	Rooster comb	0.55 ml	32G½
Hylaform		0.55 ml	30G½
Hylaform Plus		0.55 ml	27G½
Beauty Gel (yes/no):			
Beauty Gel	Bacterial fermentation	1 ml	32G½
Beauty Sphere (HA + dextran)		1 ml	30G
Hyaluderm (yes/no):			
Hyaluderm (weak reticulated HA)	Bacterial fermentation	1 ml	30G
Dethail (2005/no):			
Dethail Coilingel	Bacterial fermentation	1 ml	30G½
Dethail Lastingel		1 ml	27G½
Esthelis (2004/no):			
Esthelis Basic	Bacterial fermentation	0.6 ml	27G½
Esthelis Men		0.6 ml	27G½
Esthelis Soft		0.6 ml	30G½
Hydra Fill (yes/no):			
Hydra Fill 1	Bacterial fermentation	0.6 ml	30G½
Hydra Fill 2		0.6 ml	27G½
Hydra Fill 3		0.8 ml	27G½
Juvéderm (2000, France/no):			
Juvéderm 18	Bacterial fermentation	0.6 ml	30G½
Juvéderm 24		0.6 ml	27G½
Juvéderm 30		0.6 or 0.8 ml	27G½
Juvéderm 24HV		0.8 ml	30G½
Juvéderm 30HV		0.8 ml	30G½
Mac Dermal (yes/no):			
Mac Dermol R	Bacterial fermentation	0.6 ml	30G½
Matridur (yes/no):			
Matridex (HA + dextran)	Bacterial fermentation	1 ml	
Matridur		0.6 ml	
Puragen (2005/no):			
Puragen	Bacterial fermentation		
Rofilan (yes/no):			
Rofilan Hylan Gel	Bacterial fermentation	1 ml	
Reviderm Intra (HA + dextran)			

Table 6.6 continued

Product (CE marking/FDA approval)	*Origin*	*Syringe*	*Needle*
Restylane (1996, Sweden/yes, 2003):			
Restylane Fine Line	Bacterial fermentation	0.4 ml	31G
Restylane		0.7 or 0.4 ml	30G
Perlane		0.7 ml	27G
Restylane SubQ		2 ml	
Surgiderm (2005/no):			
Surgiderm 18	Bacterial fermentation	0.8 ml	30G½
Surgiderm 30		0.8 ml	27G
Surgiderm 24XP		0.8 ml	27G
Surgiderm 30XP		0.8 ml	30G½
Surgilips		0.6 ml	27G
Voluma (2005/no):			
Voluma	Bacterial fermentation	2 ml	21G

- Dethail Coilingel is slightly crosslinked HA, in one 1 ml syringe with two 30-gauge, ½-inch needles
- Dethail Lastingel is more strongly crosslinked HA, in one 1 ml syringe with two 27-gauge, ½-inch needles

Esthelis

Esthelis (Anteis SA, France; distributed in France by Anteis France) received its CE mark in 2004 but does not have FDA approval. The material is marketed in three forms:

- Esthelis Soft is slightly crosslinked HA, in two 0.6 ml syringes with two 30-gauge, ½-inch needles
- Esthelis Basic is more strongly crosslinked HA, in two 0.6 ml syringes with two 27-gauge, ½-inch needles
- Esthelis Men is the same as Esthelis Basic, but marketed for male patients

Hyaluderm

Hyaluderm (LCA Pharmaceutical) has received its CE mark but does not have FDA approval. It is marketed as:

- Hyaluderm which is slightly crosslinked HA, in one 1 ml syringe with a 30-gauge needle

Hydra Fill

Hydra Fill (Cornéal; distributed in France by Inamed Aesthetic) received its CE mark in 2002 but does not have FDA approval. It is marketed in five forms:

- Hydra Fill Grade 1 is slightly crosslinked HA in two 0.6 ml syringes with four 30-gauge, ½-inch needles
- Hydra Fill Grade 2 is more strongly crosslinked HA in two 0.6 ml syringes with four 27-gauge, ½-inch needles
- Hydra Fill Grade 3 is even more strongly crosslinked HA in two 0.8 ml syringes with four 27-gauge, ½-inch needles
- Hydra Fill Softline
- Hydra Fill Softline Max

Juvéderm

Juvéderm (Cornéal; distributed in France by Cornéal) received its CE mark in 2000; US FDA studies are ongoing. It is marketed in five forms:

- Juvéderm 18 is slightly crosslinked HA in a 0.6 ml syringe with a 30-gauge, ½-inch needle
- Juvéderm 24 is more strongly crosslinked HA in a 0.6 ml syringe with a 27-gauge, ½-inch needle
- Juvéderm 30 is even more strongly crosslinked HA in a 0.6 ml or 0.8 ml syringe with a 27-gauge, ½-inch needle
- Juvéderm 24HV is very strongly crosslinked, and highly viscous, in a 0.8 ml syringe with a 30-gauge, ½-inch needle
- Juvéderm 30HV is yet more strongly crosslinked, and highly viscous, in a 0.8 ml syringe with a 30-gauge, ½-inch needle

Mac Dermol

Mac Dermol (Orgév, France; distributed in France by La Centrale des Peeling) has received its CE mark but does not have FDA approval. It is marketed as:

- Mac Dermol, which is slightly crosslinked HA in a 0.6 ml syringe with a 30-gauge, ½-inch needle

Matridur

Matridur (bioPolymer Gmbh, Germany; distributed in France by Florelle) has received its CE mark but does not have FDA approval. It is marketed in two forms:

- Matridur is slightly crosslinked HA in a 0.6 ml syringe
- Matridex is HA together with dextran in a 1 ml syringe

Puragen

Puragen (Mentor, USA) received its CE mark in 2005 but does not have FDA approval. It is marketed as:

- Puragen, which is a double crosslinked HA – this may allow better resistance to degradation

Rofilan

Rofilan (Rofil Medical International, Netherlands; distributed in France by Rofil Medical International) has received its CE mark but does not have FDA approval. It is marketed in two forms:

- Reviderm Intra is HA with associated dextran
- Rofilan Hylan Gel

Restylane

Restylane (Q-Med, Sweden; distributed in France by Q-Med) received its CE mark in 1996 and FDA approval in 2003. It is marketed in Europe in three forms (plus Restylane Sub-Q: see below):

- Restylane Fine Line: 200 000 particles/ml in a 0.4 ml syringe with a 31-gauge needle
- Restylan: 100 000 particles/ml in a 0.4 ml or 0.7 ml syringe with a 30-gauge needle
- Perlane: 10 000 particles/ml (more viscous than Restylane) in a 0.7 ml syringe with a 27-gauge needle

Surgiderm

Surgiderm (Cornéal; distributed in France by Cornéal Development) received its CE mark in 2005 but does not have FDA approval. It is marketed in five forms:

- Surgiderm 18 is slightly crosslinked HA in a 0.8 ml syringe with a 30-gauge, $\frac{1}{2}$-inch needle
- Surgiderm 30 is more strongly crosslinked HA in a 0.8 ml syringe with a 27-gauge needle
- Surgiderm 24XP is more strongly crosslinked (similar to Surgiderm 30) plus XP technology
- Surgiderm 30XP is even more strongly crosslinked HA, marketed in a 0.8 ml syringe with a 30-gauge, $\frac{1}{2}$-inch needle
- Surgilips is marketed specifically for lips, in a 0.6 ml syringe with a 37-gauge needle

Theosyal

Theosyal (Theoxane, Switzerland; distributed in France by Theoxane) received its CE mark in 2004 but does not have FDA approval.

Visagel

Visagel (Dermatech, Germany; distributed in France by Dermatech) received its CE mark in 2005 but does not have FDA approval.

Volumetric Products

Restylane

Restylane Sub-Q (Q-Med, Sweden; distributed in France by Q-Med) received its CE mark in 2004 but does not have FDA approval. Its reticulation is chemical. According to the laboratory's documentation, it does not contain any protein residue, and its rate of stabilization should be identical to the other Restylane (NASHA process) products, differing only in the size and number of the particles. The product is marketed in a 2 ml syringe, injected using an 18- or 16-gauge nozzle.

Voluma

Voluma (Cornéal; distributed in France by Cornéal) received its CE mark in 2005 but does not have FDA approval. Its reticulation is chemical, and according to laboratory documentation does not have any protein residue. The product is marketed in a 2 ml syringe injected with a 21-gauge nozzle.

Non-Linked Mesotherapy Products

The following HAs are used in mesotherapy rather than generally for true filling.

Hyaluronic Acids of Animal Origin

- Achyal (Tetec-Meiji Farma, Japan; distributed in France by Filorga) has received a CE mark but does not have FDA approval. This is a non-linked HA
- IAL System (Phitogen; distributed in France by Phitogen France) received its CE mark in 2005 but does not have FDA approval. This is marketed in 0.6 and 1.0 ml syringes with a 30-gauge needle

Hyaluronic Acids Resulting from Bacterial Fermentation

- Hyaluderm (LCA Pharmaceutical; distributed in France by LCA Pharmaceutical) has received a CE mark but does not have FDA approval
- Juvélift (Cornéal; distributed in France by LEA Derm) received its CE mark in 2004 but does not have FDA approval. This is marketed in a 0.55 ml syringe with a 30-gauge, $\frac{1}{2}$-inch needle
- Mac Dermol (Orgév; distributed in France by the Centrale des Peelings) has received a CE mark but does not have FDA approval. This is marketed in two forms:
  - Mac Dermol S is a non-linked HA
  - Mac Dermol Bio is a non-linked HA with associated chondroitin sulfate
- Restylane Touch Line (Q-Med; distributed in France by Q-Med) has received a CE mark but does not have FDA approval. This is marketed in a 0.5 ml syringe with a 30-gauge needle. It is now also available in a new presentation called Vital Restylane, marketed in a 1 ml syringe
- Revitacare (Revitacare Biorevitalisation, France; distributed in France by

Revitacare) received its CE mark in 2004 but does not have FDA approval. This is marketed as 4 ml of HA to be diluted in 10 ml of multivitamins

Hyaluronic Acid with Associated Vectors

- Dermadeep (Biocristal France; distributed in France by Derma Tech) received its CE mark in 1999 but does not have FDA approval. This contains an association of 40% acrylic hydrogel (particles of 80–110 μmol) and 60% slightly crosslinked bacterial fermentation-derived HA, marketed in a 1.2 ml syringe with a 26-gauge, ½-inch needle
- Dermalive (Biocristal France; distributed in France by Derma Tech) received its CE mark in 1998 but does not have FDA approval. This contains an association of 40% acrylic hydrogel (particles of 45–65 μmol) and 60% of slightly crosslinked bacterial fermentation-derived HA, marketed in a 0.8 ml syringe with a 27-gauge, ½-inch needle

Finally, it should be noted that most laboratories manufacturing HAs do not specify the presence of protein-associated residues. Only the manufacturers of Restylane and Hylaform have done this. This is important because the incidence of filler-related reactions may be related to these protein residues. There has been extensive research and considerable clinical experience associated with both products. Currently these two fillers, as well as Juvéderm and Surgiderm, are the most popular HA products in Europe.

COMPLICATIONS OF BIODEGRADABLE ABSORBABLE PRODUCTS SEEN IN EUROPE

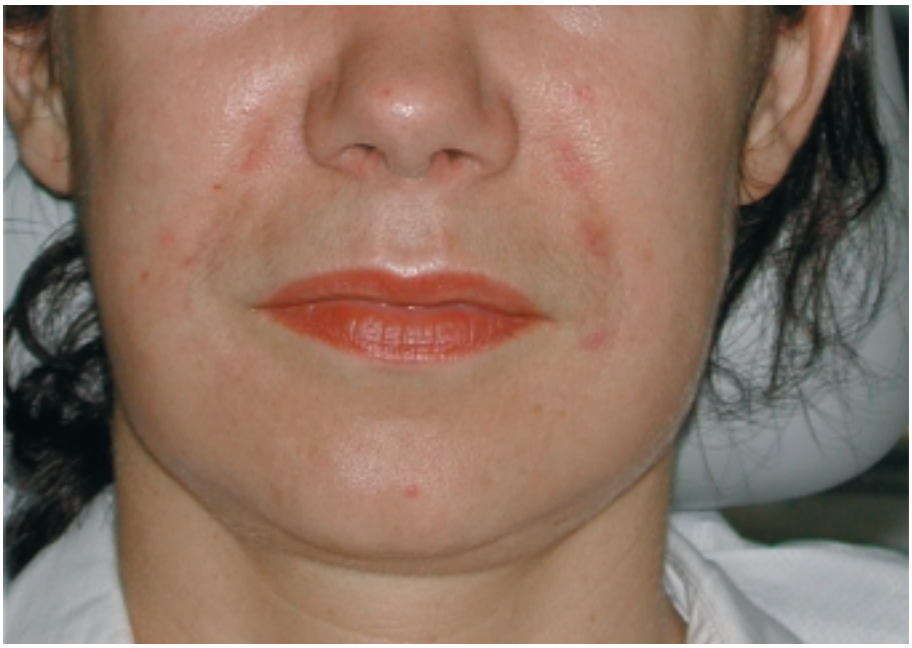
The two commonly used biodegradable products are collagen and HAs. Complications can occur from any filler. It is important to recognize potential complications, attempt to avoid them, and finally treat them when possible.

Immediate Reactions

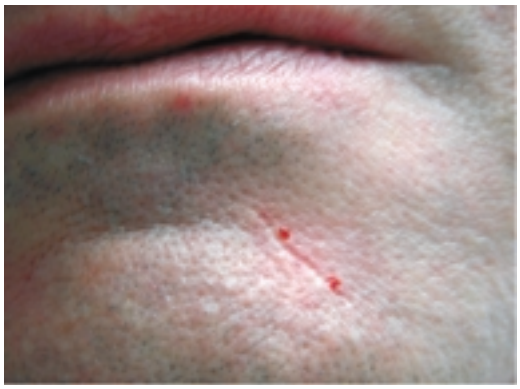
During or immediately after injection, the following can appear:

- erythema, which appears to be more common after HA injections than after collagen injections (Figure 6.1a)
- slight bleeding at injection sites – most common at certain locations, such as the peribuccal and oral commissure regions (Figure 6.1b)
- edema
- ecchymosis
- pain, pruritis, or skin hypersensitivity at injection site

These immediate reactions generally disappear within 72 hours and are very common. Many measures are available to prevent or to stop the progression



(a)



(b)

Figure 6.1. Erythema appears to be more frequent with hyaluronic acid products than with collagens: (a) inflammatory general reaction and erythema, disappearing within the following 8 days; (b) bleeding at several points. Courtesy of B. Ascher

of these side effects. These include homeopathic granules (Apis and Arnica) and creams containing vitamin K (Auriderm OX, Auriga Laboratory). Some have recommended the immediate application of a steroid-based cream (Epithelial HA, Sensibio Bioderma) and/or the use of cold packs on the injected areas to minimize short-term complications. Finally, some authors[9] suggest that all anticoagulation, including aspirin, be stopped at least four days before treatment. This, along with good injection techniques, makes the avoidance of these side effects more likely.

When dermal fillers are injected into the lips, an inflammatory sensitive edema can appear in less than 12 hours. This may persist from 2 to 7 days. Its disappearance is facilitated by the use of topical steroids.[10]

Longer-Lasting Problems

Papules or fine white lines, palpable or visible nodes, at the injection site generally represent poor technique. Either the filler has been injected too superficially or was poorly selected for that location (for example a product that was too concentrated or too crosslinked for the area to be corrected). An immediate and vigorous massage, repeated daily for several days, may help disperse the filler material. However, some papules can persist for months.

Bluish-gray, linear, painless pigmentation has been described after HA injection (Figure 6.2). This pigmentation usually disappears within 3–6 months, but can last for up to 1 year. Further injections to the same area are not recommended, as this may lead to permanent pigmentation. The cause of this pigmentation is unknown and there is no known treatment. At best, cover-up products are suggested. In Europe, the principal products to mask these colors are Color Control (Cosmodex), Couvrance (Avene), Dermablend (Vichy), and Unifiance (Posay Rock).

Insufficient correction of the treated side can simply be improved with reinjection of the filler soon after the initial injection.

Overcorrection with frankly visible implant can last for about 1 year. This is best avoided with correct technique.

More Serious Semi-delayed Complications

These occur in the days following the injection.

- Abscesses at the injection site are generally related to poor sterile technique.
- Hematoma and ecchymoses appear in the hours following the injection, usually localized to the peribuccal region.[11] They can be seen in numerous areas after mesotherapy.

An immediate compression with the added application of cold packs will limit this type of complication, which can last for more than 1 week.

Paraesthesia and allergy to local anesthetic are rare complications.

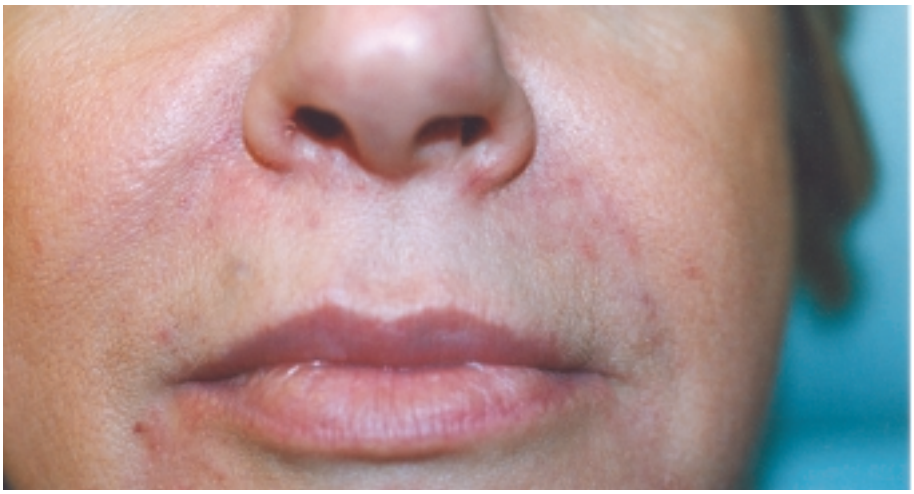


Figure 6.2. Bluish-gray, linear, painless pigmentation has been described after HA injection. This pigmentation usually disappears within 3–6 months, but can last for up to 1 year. It is a contraindication for all new injections before complete disappearance of the pigmentation. The cause of this pigmentation is unknown and there is no known treatment. At best, cover-up products are suggested. Courtesy of Martine Baspeyras.

Delayed Complications

These generally appear at least a day after the injection. These reactions are quite varied in nature and tend to be localized within the injection site. They have been reported with both bovine collagen (see Chapters 2 and 8) and HAs.[12,13] They can take the following forms:[11,14]

- intense and hardened erythema
- non-specific blue–purple granulomas
- hardened folliculitis
- pseudocysts and nodes

It should be noted that these reactions are more frequent with collagen than with HA. They generally appear 1–4 weeks after injection (even later reactions have been reported with collagen). They can appear at the time of the first injection, but also after any later injection (Figure 6.3).

These complications must be treated as soon as possible. With the appearance of erythema, a local and perhaps even a systemic steroid must be prescribed for 15 days. Fortunately, total disappearance of this type of complication is usual, but they can last some months. Some experts suggest that these lesions be incised or punctured to accelerate cure, but the risk of scarring is always present.[11]

These delayed local complications have been classified into two types: of immunologic and non-immunologic origin.

The immunologic reactions are thought to be delayed hypersensitivity reactions. These are T-lymphocyte-mediated and are induced by antigen present in the injected dermal filler. The specific immune reaction is due to the presence of various proteins (residues, bacteria, and impurities).

Non-immunologic local reactions such as granuloma, represent foreign body reactions (Figure 6.3), with the host's phagocytic cells producing inflammatory cytokines at the time of filler injection. These non-specific reactions cause an infiltrate around the implant. Other non-specific inflammatory reactions that have been described after HA injections are thought to be secondary to the presence of postmanufacturing residues of linkage or stabilization. Other contaminants can also be implicated in the formation of such reactions. Only Restylane and Hylaform appear to have produced rare reactions to residues – this may be because they have been on the market for a considerable time, are widely used, and have been the subjects of extensive, published safety studies. Treatment is by injection of a small amount of hyaluronidase, which leads to rapid disappearance of the granuloma.

Rare cases of necrosis have been described, particularly after collagen (Zyplast) injection into the glabellar area.[15] To date, there are no published studies documenting any case of necrosis after injection of HA.

Patient satisfaction is always an issue with any cosmetic procedure. A basic psychologic profile of patients can occasionally sort out the patient with totally unrealistic expectations.

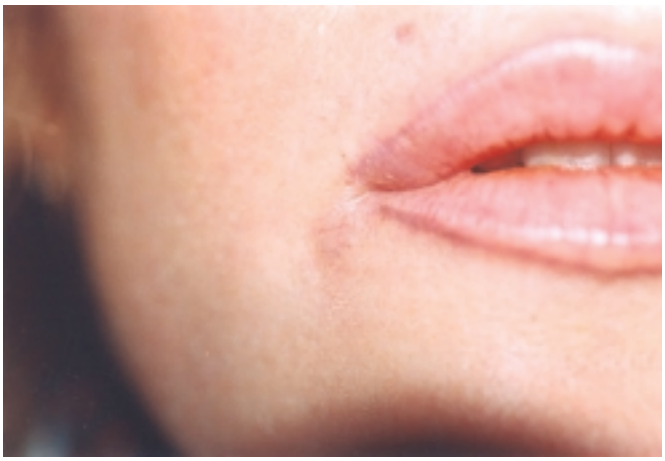
Generally, absorbable products have mild side effects and are short lasting – which is why they are generally considered as reliable and safe products. More serious side effects have been reported with the injection of absorbable products at the same site where non-absorbable products were injected. These side effects include granulomas, whose treatment is often partial and difficult.[16,17] It is therefore necessary to avoid any injection of a slowly absorbable product in a site already treated with a non-absorbable product. When granulomas appear, they are generally due to the most recent injection at the affected site.

Declaration of the Complications in France

As described above, any serious complication that may threaten the life of a patient must be declared to avoid legal repercussions. Other less severe complications should also be reported (even if this is not legally required) so that treating physicians can improve their knowledge base and potentially avoid such complications in the future.

In France, the following declarations should be made:

- at the AFSSAPS website (www.afssaps.sante.fr)
- to liability insurers, to be certain that coverage will be available



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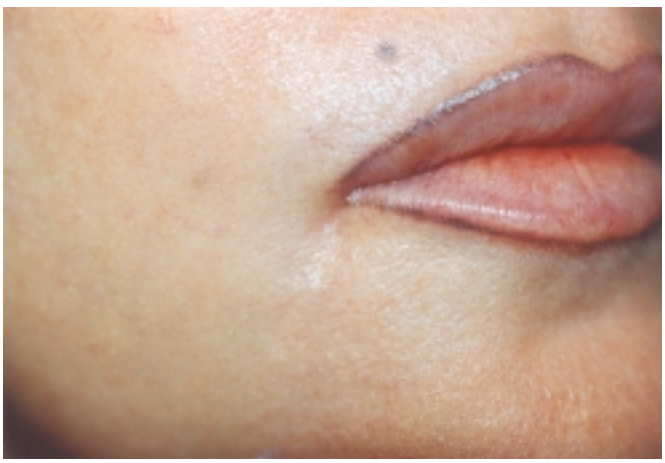

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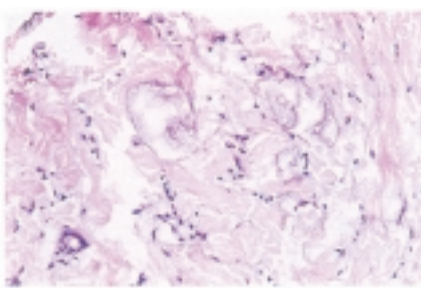

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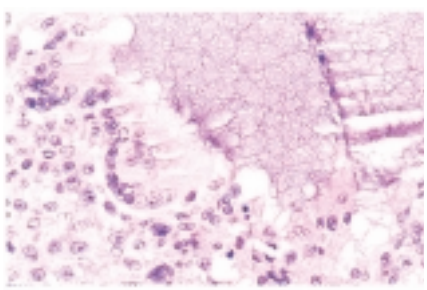

(d)

Figure 6.3. (a) Clinical representation of granuloma, representing a foreign body reaction after a hyaluronic acid filler injection. Treatment was with a small quantity of hyaluronidase and a quick resolution was seen in a few days. Such findings rarely occurred with older hyaluronic acid fillers. They are distinctly uncommon with todays purified products. (c, d) Histologic evidence of granuloma formation.

- at the VIGIPIL website – a website organized by French dermatologists that provides a registry for complications seen after the performance of esthetic medical procedures (Martine-baspeyras@wanadoo.fr)

In conclusion, side effects after HA injection are generally not severe and are usually short-lived. Finally, because, as will be described below, complications from non-absorbable products are generally more severe and long-lasting, it is best to avoid HA injections at the site of a previously injected non-degradable product.

VERY SLOWLY ABSORBABLE AND NON-ABSORBABLE DERMAL FILLERS IN EUROPE

There are a wide variety of very slowly absorbable and non-absorbable dermal fillers available in Europe.

Aquamid

This PAAG polymer gel (frozen acrylic alkylimide 2.5% gelled in 97.5% sterile water) (Contura International, Sweden/Denmark) has received a CE mark but does not have FDA approval. It is marketed as a 1 ml syringe.

Artecol

This comprises polymethyl methacrylate microspheres (PMMA) (30–60 μm) in suspension with a bovine collagen solution of 3.5% and 0.3% lidocaine (RMI, The Netherlands) and has received a CE mark but does not have FDA approval. It is marketed as four 0.5 ml syringes with a 26-gauge, $\frac{1}{2}$-inch needle.

Bio-Alcamid

Frozen acrylic alkylimide 4% gelled in 96% non-pyrogenic water (Polymekon, Italy). It has a CE mark, MDR Canadian approval and has been granted HUD (humanitarian use device) approval by the FDA for use in severe lipodystrophic hemifacial syndrome (Parry Romberg). It does not currently have FDA approval. The filler is marketed as two 1 ml (lips), one 3 ml (face), two 5 ml syringes (body), seven 3 ml syringes (Rinnova), and twenty, thirty and forty 5 ml syringes respectively (large volume) with a 19 gauge needle.

Bioinblue

Reabsorbable cross-linked polymer hydrogel with 6% high purity polyvinyl alcohol and 94% non-pyrogenic water (Polymekon, Italy). It has a CE mark, MDR Canadian approval but no FDR approval as yet. The filler is marketed as two 7 ml syringes.

Dermalive

This polymeric acrylic resin gel combining hydroxyethyl methacrylate (HEMA) with ethyl methacrylate (EMA) (45–65 μm: 40%, including 25% water in 60% of crosslinked HA) (Dermatech, France) has received a CE mark but does not have FDA approval. It is marketed as two 1 ml syringes.

Dermadeep

This polymeric acrylic resin gel combining HEMA and EMA (80–110 μm: 40%, including 25% water in 60% of crosslinked HA) (Dermatech, France) has received a CE mark but does not have FDA approval. It is marketed as two 1.2 ml syringes with 26-gauge, ½-inch needles.

Eutrophill

This comprises microspheres of polyvinyl alcohol with a polyacrylamide gel (PAAG) (ProCytech, France) and has received a CE mark but does not have FDA approval. It is marketed either as two 1 ml syringes or two 2.5 ml syringes.

Evolution

This comprises microspheres of polyvinyl alcohol/frozen acrylamide (PAAG) (ProCytech, France) and has received a CE mark but does not have FDA approval. It is marketed as either one 1 ml syringe or two 0.5 ml syringes, with 27- or 30-gauge needles.

Isolagen

This suspension of autologous fibroblasts obtained by culturing a punch biopsy of 3 mm retro-auricular skin (developed by Isolagen, USA) has received a CE mark and FDA studies are currently underway. The biopsy must be sent to the laboratory within 24 hours; 1.2 ml of the product can be formed in eight weeks. An additional 1.2 ml of additional material can be obtained every 2–3 weeks. The cell line can be stored indefinitely in liquid nitrogen by the laboratory.

New-Fill/Sculptra

This is a hydrogel of poly-L-lactic acid (PLLA). See the description in Chapter 5 – the European product is identical to the US one.

Outline

This polymeric acrylamide resin (PAAG) gel (30% in 70% sterile water) (Procytech, France) has received a CE mark but does not have FDA approval. It is marketed in three forms:

- Outline Fine: either a single 1 ml or two 0.5 ml syringes with either 27- or 30-gauge needles
- Original Outline: either a single 1 ml or two 0.5 ml syringes with either 27- or 30-gauge needles
- Outline Ultra: either a single 1 ml or two 0.5 ml syringes with either 27- or 30-gauge needles

Radiesse

This comprises microspheres of calcium hydroxyapatite in a carboxymethylcellulose gel (see Chapter 4) (Bioform, USA), it has received a CE mark and is FDA-approved. It is marketed as a 1.3 ml syringe.

Reviderm/Beautysphere

This comprises HA plus microspheres of dextran (RMI, The Netherlands) and has received a CE mark but does not have FDA approval.

COMPLICATIONS OF SLOWLY ABSORBABLE AND NON-DEGRADABLE PRODUCTS SEEN IN EUROPE

Complications of Slowly Absorbable Products

Reactions can be very different depending on the duration between the injection and the beginning of the clinical reaction.

Immediate and Minor Reactions

These are often related to improper injection technique. They include punctiform hematoma (which can sometimes be lessened by the application of vitamin K before and/or immediately after injection) and erythema or light edema along the injected pathway. It should be noted that these reactions are frequent and transient. They often disappear within 48–72 hours following the procedure.

Semi-delayed Reactions

After too superficial an injection, one can observe a visible white line, which disappears only with absorption of the product. In some cases, the reactions seen with slowly absorbable products are identical to those seen with fully biogradable products. Some of the longer-lasting reactions may be seen with products such as dextran associated with HA in these fillers.

Delayed Reactions

Some products such as PLLA that are slowly absorbed are associated with the late development of purplish, very hard, nodules, which can appear 6–24 months after injection. These appear to be associated with the use of an

overly concentrated product and superficial injections. These reactions are likely to be particularly intense in the areas where the skin is thin and fine and the product is injected superficially. Thus, these products are not recommended in the periorbital and peribuccal areas, where the skin is too thin. It would also appear preferable to avoid injections at the level of the jowls, where the epidermis is thin and the skin is 'folded'.

Treating these nodular granulomatous lesions with either local and/or systemic steroids does not provide much improvement. Even injections of 5-fluorouracil (5-FU) directly into the nodules do not seem to help.

Sometimes, when used early on in inflammatory lesions, 2 months of twice-daily hydroxychloroquine hydrochloride can often result in a reduction of the inflammatory process.

Complications of Non-degradable Filler Materials

Non-degradable materials are responsible for a variety of immediate and delayed reactions.

Immediate Reactions

These can be inflammatory, papulonodular, blue–purple lesions. They are transitory and disappear in a few days to a few weeks.

Delayed Reactions[18,19]

In general, delayed reactions are foreign body granulomas. Diagnosis can be made both clinically and following biopsy. Such granulomatous reactions are probably not rare, but may remain clinically latent. However, in certain cases, the granulomatosus reaction can be clinically very significant, leading to bulky, palpable, visible, sometimes painful, draining lesions.

PMMA fillers can cause granulomas that appear some time (6 months–2 years) after injection. These tend to be bluish-purple in appearance, and show little spontaneous improvement. They may respond to intranodular injections of steroids (Figure 6.2).[10]

Acrylic hydrogel fillers have become very popular over the last few years. They have been reported to cause frequent granulomas, which can present as hard nodules that can be of stony consistency with or without an overlying erythematous color. They are often very visible and easily palpable between two fingers, and are most commonly seen around the lips. Because of their non-absorbable nature, these nodules do not (or very minimally) regress spontaneously. Unfortunately, treatment is generally very disappointing. Injections of steroids into the lesions cause minimal improvement that can be of short duration even after multiple injections.

Intralesional injections of 5-FU or a combination of steroids and 5-FU have also led to disappointing results. Moreover, these injections may exacerbate the appearance of the purplish nodules. It is often for these reasons that patients desire surgical excision, where the immediate result is often satisfac-

tory, but sometimes can lead to further permanent scars. Unfortunately, after excision, nodules may reappear at the periphery of the excision. This may be related to the migration of acrylic particles at the time of treatment. Some investigators have used both CO_2 and long-pulsed erbium lasers, which seem to give rather satisfactory results. Others have used lipofilling, with encouraging results. Finally, in certain rare cases, the nodules can resolve by spontaneous extrusion.

With polyacrylamide gel fillers, microbe-free abscesses can develop a few weeks after injection. These tend to last from 3 to 4 weeks before spontaneous healing.

The use of alkylimides can result in the late appearance of granulomas. In this case, surgical excision is usually required.

Dimethylsiloxane has a formula almost identical to that of a silicone fluid that was used for filling of wrinkles and gave rise to some nodular reactions, and is now prohibited in France.[20–23]

CONCLUSIONS

The majority of European fillers in current use have been reviewed. New fillers are constantly coming onto the European market. Thorough understanding of their pharmacology, clinical results and associated complications is necessary before they should be used widely by cosmetic surgeons.

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