

Topical Report

Injectable products to fill wrinkles

1 –Contextual elements

Injectable wrinkle fillers are mostly used to treat facial wrinkles by injecting a gel into the skin (dermis). They respond to the definition of a long-term, invasive, surgical device since they are introduced invasively into the skin using a syringe and are intended to remain in place for at least thirty days. They also follow the same regulations as implants in terms of classification.

They have been developed as a result of the extended use of devices used to fill volumes of the body. These devices are qualified by their ability to change the patient's anatomy and are used for reconstructive purposes in the treatment, for instance, of facial lipoatrophy, debilitating scars or morphological asymmetry.

The market for these devices is constantly developing, accounting for a sales volume of over 3 000 000 syringes in France between 2003 and 2008, i.e. 600 000 syringes by year. Approximately 100 products are currently placed on the market by 35 manufacturers in France.

Evaluation of the benefit/risk ratio relating to a medical device in a medical intention is different from that of a device used solely for aesthetic purposes such as products for wrinkles treatment.

Although the benefit linked with a device in a medical application is objective, measurable and has a direct impact on the patient's health, the success of an aesthetic procedure is mainly associated with a person's feelings.

As for risk analysis, a significant risk that is deemed acceptable in medical terms would not be classed as such simply in order to aesthetic improvement.

The characteristic "Invasive" and their wide involvement in healthy subjects suggest potential complications. Consequently, these devices must be strictly monitored by the health authorities in terms of market and vigilance checks. This has been the situation since an initial market control was carried out in 2002.

Product diversity coupled with an increase in the number of manufacturers has led ANSM (French Agency for the Safety of Healthcare Products) in conjunction with outside experts to re-examine devices and their inherent risks over the last two years.

Products containing hyaluronic acid

The first injectable wrinkle fillers products contained collagen of bovine origin. A prior skin test was mandatory in order to prevent allergic effects. Before long, industrialists strived to create slightly non-allergenic products, hence the arrival of the first hyaluronic acid (HA)-based formulations. In fact, HA is a natural component of connective tissue and synovial fluid in human and in numerous animal species. In the injectable wrinkle fillers application, it is not used in its natural form.

HA was initially extracted from cock's comb. It is nowadays produced by bacterial biofermentation essentially to boost productivity. To increase the lasting effect of the filling product, the HA produced in this way is chemically modified by molecules known as "cross-linking agents". It differs from the HA naturally found in cells within the body.

Sterility and injection

Injectable wrinkle fillers products are mostly available in the form of pre-filled, ready-to-use gel syringes. They are sterile and, as for any injectable solution, they must satisfy European Pharmacopoeia requirements, i.e. they must be clear (no suspended particles) and apyrogenic. Some products have to be dissolved prior to injection.

Injection of the product into the skin is an "intra-dermal" process but warrants compliance with the instructions given in the package insert particularly with regard to the injection site, which depends on the thickness of the skin, vascularisation of the injected area and the nature of the main material used in the filling gel.

2 - Classification of injectable wrinkle fillers

Most of these products will be broken down and then eliminated by the body. Some of them, however, may or may not be entirely eliminated and could therefore remain indefinitely, either in full or in part, in the tissue.

So far, no European nomenclature has been proposed that would help professionals using these products to identify the duration of their effects and the risks associated with their use.

Based on published data, the agency therefore proposes to classify these devices in an attempt to provide better information for professionals and the general public alike. Depending on the components, injectable wrinkle fillers have a specific duration of action and elimination process.

These products can thus be classed in three categories depending essentially on the length of time they remain in the body: absorbable, slowly absorbable and non-absorbable products.

“Absorbable” and “slowly absorbable” products are those that are naturally eliminated by the body over time compared to “non-absorbable” products which permanently remain in the skin.

Absorbable products

These are mostly derived from hyaluronic acids of animal origin or produced by biofermentation, and can undergo chemical changes causing them to remain within the body for 3 to 6 months.

Slowly absorbable products

Their effect persists for 6 months to 2 years. Some substances have already been used in medical applications (hydroxyapatite, alginate, etc.) without any guarantee that they are perfectly safe within the skin.

Non-absorbable products

They are permanently present within the body. They can be produced, for instance, from acrylic or methacrylic polymers or polyacrylamid gel and possibly combined with an absorbable material (hyaluronic acid, collagen, etc.). If the product can be extracted in certain cases, only partial extraction will be feasible.

The following table provides a non-exhaustive list of materials used in the composition of injectable wrinkle fillers currently or previously on the French market.

	ABSORBABLE SUBSTANCES	SLOWLY ABSORBABLE SUBSTANCES	NON-ABSORBABLE SUBSTANCES
Duration of presence within the body	3 -6 months	6 -24 months	permanently
Composition	- Hyaluronic acid (depending on its characteristics) -Alginate (depending on its characteristics)		-Acrylic polymers (polyacrylamide)
	-Collagen	-Hyaluronic acid + hypromellose	-Methacrylic polymers (methyl polymethacrylate) (PMMA) + collagen
		-TriCalcium Phosphate (TCP) + Hyaluronic acid	-Polymer particles (poly(hydroxyethyl methacrylate-co-ethyl methacrylate) (PHEMA-co-EMA)-
		- Calcium hydroxyapatite (CaHa)	
		-Polylactic acid	
		-Dextran microbead + Hyaluronic acid	

Non-exhaustive list of materials used in the composition of injectable wrinkle fillers

It should be noted that injectable (non-absorbable) liquid silicone has been prohibited in France since 2001 following a decision taken on 31 May 2000, published in official journal to June, 09th, 2000.

3 –Placing on the market

As medical devices, injectable wrinkle fillers must satisfy the essential requirements of the European Directive 93/42/EEC modified by 2007/47/EC. Thus Manufacturers must therefore submit their products for a safety and performance evaluation by an organism so-called “notified” body, i.e. an organisation enable of issuing a CE certificate that the manufacturer needs to establish EC declaration of conformity. The latter will allow the manufacturer to affix the CE marking to his product. This type of organism is controlled by a competent national authority (ANSM in France) within the EU.

Demonstration of compliance with essential requirements must include preclinical data (*in-vitro* laboratory tests and laboratory animal experiments). A clinical evaluation of the performance and safety of the device must also be carried out.

The preclinical data recorded prior to tests in humans provide predictive information regarding the risks associated with the use of medical devices but cannot guarantee their total safety.

International guidelines such as standards essentially list the pre-clinical tests to be carried out by the manufacturer in order to guarantee the safety and performance of the medical device. These include ISO standard 10993 relating to the biocompatibility of medical devices.

ANSM is on going writing a draft for a reference document to apply standard ISO 10993 specifically to injectable wrinkle fillers.

Directive 2007/47/EC applicable to 21 March 2010 reinforces requirements in terms of clinical evaluation and insists on the collection of additional data following the product's market launch.

The clinical data relating to injectable wrinkle fillers in humans are not sufficient to guarantee the safety in use of a given product essentially because of the small cohorts involved and the delayed onset of certain serious side effects such as granuloma (appearing after a few months to several years). In fact, the two limiting parameters in these types of clinical trial are the reduced number of subjects recruited for the trials and the limited duration of the study.

Clinical trials on absorbable products generally are carried out in 150 subjects over 3 to 6 months during which time the consequences of repeat injections are not evaluated.

Regarding the permanent products, this is usually an identical cohort and duration of study varies from one product to another but generally not exceeding three years, duration much lower than that observed at the onset of some granulomas (5-10 years).

Consequently, with the support of ANSM experts, the agency is preparing a reference document governing the implementation of a clinical trial and a post-market survey carrying on injectable wrinkle fillers in particular to measure the incidence of adverse events.

4-Surveillance

As medical devices, injectable wrinkle fillers must bear the CE mark, attesting of conformity, claimed by the manufacturer, with European directive requirements 93/42/EEC, modified by 2007/47/EC. The CE mark is a guarantee in the free movement on the European market.

Injectable wrinkle fillers are medical devices that pose a high potential risk to human health, thus class IIb/III devices. These classes of devices are the subject of communication of placing on the French market sent to ANSM by the manufacturer, or authorised representative or distributor.

List of injectable wrinkle fillers communicated to ANSM (see french version).

The manufacturer is responsible for placing the device on the market. However, the EU competent authorities are responsible for market surveillance of medical devices.

As a general rule for all medical devices, the agency can :

- carry out market controls on products dossiers and focuses in particular on new products,
- inspect manufacturers,
- carry out laboratory tests on samples or directly on products already on the market.

In the case of the agency finds that a device can compromise health and / or safety of patients, users or others, she can take all appropriate interim measures to withdraw such devices from the market, prohibit or restrict their placing on the market.

The characteristics of an injectable wrinkle filler bearing a CE medical mark

An injectable wrinkle filler complies with current legislation and bears the CE mark relating to medical devices comprising at least:

- On the packaging and instruction for use, the  pictogram with four numbers that define the organism that issued CE mark for the product,
- Instructions for use

The agency invites health care professionals to regularly consult the communication list relating to the placing on the market of injectable wrinkle filler on the French market.

Counterfeiting and falsification

Purchased on the Internet, these products are generally imported into France by post, which makes their detection difficult. Their presence on illegal way means that they escape from the regular controls carried out by the health authorities.

Medical devices purchased on the Internet, even if they are available under a brand name that is already marketed, are not always the products affixing the CE mark. Under these conditions, neither the quality nor the storage conditions under which the medical devices purchased on the Internet should be guaranteed.

The person receiving is exposed to receive counterfeit or poor quality medical devices which may be outdated or altered as a result of inappropriate storage or transport conditions. Similarly, the raw materials used in these products can also be counterfeit or of mediocre quality.

ANSM post information on the Internet as soon as it becomes aware of counterfeit products (RESTYLANE communication [\(see french version\)](#)).

Products distributed during public events (aesthetic congresses, salons, etc.)

Products distributed during public events may not, in some cases, affix yet the CE mark and/or their placing on the market may not yet have been communicated to ANSM. The labelling of these products must be unambiguous and indicate that they are not intended for use in humans.

A given product, as a free sample, for its use, must have received the CE mark.

Particular attention and vigilance are therefore warranted in such cases.

5-The main risks associated with injectable wrinkle filler

The injection of these devices into the skin constitutes the introduction of a foreign body likely to trigger a skin reaction. These reactions are mostly temporary (redness, oedema, etc.) but can be affected by numerous external factors (nature of product used, injection technique, injection site, number of injections) and factors specific to individual (safety/tolerance and the person's medical history).

The main risks associated with their use are listed in the product's instructions for use (haematoma, erythema, etc.).

Less common risks, such as the onset of granuloma, are chiefly associated with slowly absorbable and non-absorbable products. Granuloma may develop several months or even several years after the product has been implanted injected.

Based on available data, side effects affect between 0.1 and 1% of injected persons:

Reactions	Side effects	Estimated duration
Immediate (1d-15d)	▪ Haematoma, erythema, oedema	8 d
Semi-delayed (15d-3 months)	▪ Infection (relating to conditions of asepsis) ▪ Necrosis ▪ Non-specific inflammation	1-6 months 3 months
Delayed (3-24 months)	▪ Allergy, erythema ▪ Pigmentation	1-12 months
Delayed (rare) (> 3 months – x years)	▪ Granuloma	X months- permanent

Non-exhaustive list of side effects associated with the use of injectable wrinkle filler

Focus on non-absorbable injectable wrinkle filler

The Agency is not currently advising the use of non-absorbable products in the aesthetic purpose given the risk of extremely delayed, uncontrollable, serious adverse effects. The risk of onset of such events, after several years, may be increased by the injection of various products or other treatments for aesthetic purposes.

Experience with the use of non-absorbable injectable products has shown that the onset of delayed, product-related complications such as granuloma is generally due to the permanent presence of the product. This type of inflammatory reaction is more promoted if the product is permanently present in the skin.

When these delayed reactions appear, their effects, like the product, tend to be permanent, which makes them difficult to treat. In view of the experience gained with certain non-absorbable products such as DERMALIVE®, which was withdrawn from the market by the manufacturer, DERMATECH, in 2007, and was responsible for the onset of delayed granuloma (2 to 10 years post-injection), the patient must be informed that non-absorbable products are not recommended for aesthetic purpose.

These products are not forbidden in Europe at the present time since their use may be justified in certain cases, essentially reconstructive surgery, and with any complications observed are essentially local.

Moreover, published data relating to the evaluation of the safety in use of these products are insufficient and related complications are extremely difficult to obtain vigilance system report, essentially because of the wide scatter of persons involved.

Based on current knowledge, the frequency of risks associated with the use of injectable wrinkle filler is difficult to define for the following reasons:

- Inadequate timeframe: this is an emerging market many new products and materials are available,
- Lack of vigilance system reports: the considerable scatter of persons receiving injectable wrinkle filler makes it difficult to collect relevant data reflecting the actual number of incidents associated with the injection of these products
- The onset of side effects is very often linked to a specific product and not to a category of products. Furthermore, in some cases, the risks are associated with the manufacturing process (e.g.: contaminants) as well as the rheological properties of the device (e.g.: form, viscosity, etc.).

6- Trace back and vigilance system

Given their invasive characteristics and the considerable scatter of subjects undergoing aesthetic procedures, injectable wrinkle filler must be traced back during each injection in the same way as medical devices, as stated in [Decree No. 2006-1497](#) and [Order dated of 2007, January, 26th](#).

Thus a person receiving an injection must be told of the characteristics of the injected product (trade name, manufacturer and batch number) and the circumstances of the injection (clinician, location, intention and injection site).

Vigilance system seeks to prevent the recurrence of incidents and the risk of serious adverse events involving medical devices. With this in mind, it is important that healthcare professional, that are legally obliged to do so, report these serious adverse events to ANSM such that appropriate preventive or corrective measures can be taken.

The injected persons themselves can inform the agency of the type of event but generally do so via their clinician.

Two forms, especially designed for reporting this type of event, and intended for persons and healthcare professionals, will soon be available on the ANSM Internet site.

These reports will be evaluated internally involving outside experts who must assess the direct implication of the medical device in question. The agency's mission is then to issue warnings and check that corrective measures are implemented via recommendations or arrange for temporary market withdrawal if a serious danger has been recognised linking an incident with the medical device.

7 – Recommendations for clinicians and the general public

injectable wrinkle filler are defined as long-term, invasive, surgical devices. Their "invasive" characteristics imply potential complications. In addition, their use in healthy subjects and the wide scatter of these subjects in terms of aesthetic procedures warrants stringent monitoring by the health care competent authorities in terms of the circulation of information, market control and vigilance. Definitions of terms currently used in commercial brochures and technical documentation relating to injectable wrinkle filler are available in French language into the glossary on the ANSM Internet site.

Clinicians (data sheet)

At the present time, there is no regulatory framework governing the administration of injectable wrinkle filler. However, the French general health directorate is preparing a framework for aesthetic procedures.

Injections constitute a procedure with important specific technical features. At the present time, injectable wrinkle filler are generally carried out by plastic surgeons, dermatologists and clinicians who have received specific training.

Under what conditions?

Before use of injectable wrinkle filler:

- The clinician is advised to enquire about the person's medical history:
 - History of severe allergies
 - Anaphylactic reactions (acute allergic reaction)
 - Allergy to a local anaesthetic
 - Tolerance to antibiotics or corticosteroids
 - Abnormal bleeding
 - Condition of the injection site (pre-existing scars, infection, etc.)

- The clinician is advised to ask the person about earlier aesthetic treatments focusing in particular on the nature of product previously injected. Because it is not advisable to use an absorbable product after applying a non-absorbable product to the same injection site.

- The clinician is advised to select a product that complies with current legislation (CEXXX) to be injected depending on the facial area targeted, the depth and duration of the effect (information contained in the instructions for use).

- It is important to inform the person of the risks and side effects likely to occur following injection of the injectable wrinkle filler. These are summarised in the following table. It should also be noted that when delayed reactions occur, essentially after the injection of permanent products, their effects, just like the product itself, tend to be permanent. This makes them difficult to treat.

Reactions	Side effects	Estimated duration
Immediate (1d-15d)	<ul style="list-style-type: none"> ▪ Haematoma, erythema, oedema 	8 d
Semi-delayed (15d-3 months)	<ul style="list-style-type: none"> ▪ Infection (relating to conditions of asepsis) ▪ Necrosis ▪ Non-specific inflammation 	1-6 months 3 months
Delayed (3-24 months)	<ul style="list-style-type: none"> ▪ Allergy, erythema ▪ Pigmentation 	1-12 months
Delayed (rare) (> 3 months – x years)	<ul style="list-style-type: none"> ▪ Granuloma 	X months-permanent

- It is not advisable to use non-absorbable products for an aesthetic purpose : Experience with the use of non-absorbable injectable wrinkle filler has shown that the onset of delayed complications such as granuloma is generally due to the permanent presence of the product. This type of inflammatory reaction is all the more likely to develop if the product is permanent.

During and after use of injectable wrinkle filler:

- It is essential to trace back :
 - Aesthetic procedures, mainly the number of injections and the length of time between two injections,
 - The products used,
 - The facial areas targeted,
 - The volumes used,

And to store person data for a period of 15 years and to provide the patient with all of this information in the form of an “aesthetic log”.

- Any side effect must be reported to ANSM

General public (data sheet)

Who injects?

At the present time, there is no regulatory framework governing the administration of injectable wrinkle filler. However, the French general health directorate is preparing a framework for aesthetic procedures.

Injections constitute a procedure with important specific technical features. At the present time, injectable wrinkle filler are generally carried out by plastic surgeons, dermatologists and clinicians who have received specific training.

Where?

injectable wrinkle filler are intended to be injected in the skin, in a precise depth (superficial dermis, deep dermis...) and area (lips, glabella, nasolabial folds, etc.) of the face shown in the instructions for use. The injection of product at a depth other than that specified in the instructions for use and/or its use for application to any part of the body other than that specified in the instructions for use may have serious consequences on the person's health.

Under what conditions?

Before use of injectable wrinkle filler:

- The person should inform the clinician of any medical history
- The person should inform the clinician of earlier aesthetic treatments focusing in particular on the nature of product previously injected. Because it not advisable to use an absorbable product after applying a non-absorbable product to the same injection site
- It is important to know the risks and side effects that may occur after injecting an injectable wrinkle filler
- It is not advisable to use non-absorbable products for an aesthetic purpose : Experience with the use of non-absorbable injectable products has shown that the onset of delayed complications such as granuloma is generally due to the permanent presence of the product. This type of inflammatory reaction is all the more likely to develop if the product is permanent.

During and after use of injectable wrinkle filler:

- All of the documents relating to the following must be stored for a period of 15 years in a file or in an "aesthetic log".
 - Aesthetic procedures, mainly the number of injections and the length of time between two injections,
 - The products used,
 - The facial areas targeted,
 - The volumes used.
- Any undesirable effect must be reported yourself or by your clinician all kind of adverse events to ANSM.