CLINICAL EVALUATION

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1. General Details

Manufacturer:	BioScience GmbH Walsmühler Straße 18 19073 Dümmer Germany
Medical Device:	**Hyacorp MLF1** **Hyacorp MLF2** **GeneFill Contour** GMDN-Code: 17876

2. Description of the device and its intended application

HYAcorp MLF1 / MLF2 / Genefill Contour is an absorbable skin implant with a high level of purity. It is a medical device intended for single use only and is produced from a hyaluronic acid of non-animal origin. HYAcorp MLF1 / MLF2 / Genefill Contour is a sterile, apyrogenic, viscoelastic, biologically compatible (nonimmunising, non-inflammatory, non-toxic) gel implant that is insoluble in water and produced from a hyaluronic acid obtained by fermentation. Hyaluronic acid is a naturally occurring polysaccharide in the dermal matrix of human skin. The hyaluronic acid in the tissues of all higher organisms is chemically, physically and biologically identical. HYAcorp MLF1 / MLF2 / Genefill Contour is a clear viscous gel supplied in a 10 ml syringe with a Luer lock port.

The products under discussion are certified as medical devices since 2013 and are already marketed in the European Union.

Composition

The products under discussion have an identical composition. They only differ in the particle sizes of the cross-linked hyaluronic acid, and minor differences are present in viscosity.

1 mL **Hyacorp MLF1** contains:

Hyaluronic acid sodium salt	2.0 mg
Cross-linked Hylan gel	20.0 mg
Sodium chloride	6.9 mg
Water for injection ad	1.0 mL

1 mL **Hyacorp MLF2** contains:

Hyaluronic acid sodium salt	2.0 mg
Cross-linked Hylan gel	20.0 mg
Sodium chloride	6.9 mg
Water for injection ad	1.0 mL

1 mL **Genefill Contour** contains:

Hyaluronic acid sodium salt	2.0 mg
Cross-linked Hylan gel	20.0 mg
Sodium chloride	6.9 mg
Water for injection ad	1.0 mL

Physico-chemical characteristics

The products are sterile and their maximum endotoxin content is specified at < 0,025 EU/mL (LAL). Unbound BDDE is reduced to trace amounts in all products (specified < 1ppm). Further specifications are presented in the table below.

	Viscosity (mPas)	**pH-Value**	**Osmolarity (mosmol/kg)**	**Particle size (µm)**	**Degree of cross-linking (%)**	**Volume**
Hyacorp MLF1	14.000 – 20.000	7.0 – 7.2	280-360	200 – 350	0 – 20	10 mL
Hyacorp MLF2	14.000 – 20.000	7.0 – 7.2	280-360	300 – 500	0 – 20	10 mL
GeneFill Contour	14.000 – 20.000	7.0 – 7.2	280-360	200 – 350	0 – 20	10 mL

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan disaccharide composed of alternately repeating units of D-glucuronic acid and N-acetyl-D-glucosamine (Figure 2-1). It is a major component of the extracellular matrix found in many human tissues, including the skin. In contrast to other glycosaminoglycans, it occurs free and is not linked to proteins in the

dermis. The highly charged nature of HA renders it soluble and allows it to bind water extensively, which determines skin viscoelasticity. Hyaluronic acid is chemically, physically and biologically identical in the tissues of all higher organisms (Kablik, Monheit et al. 2009).

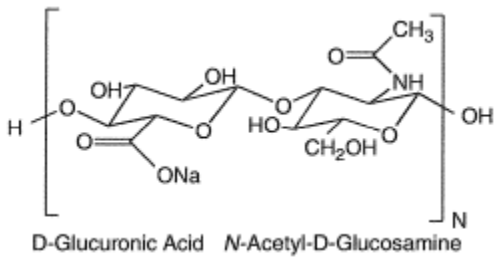

Figure 2-1 Hyaluronic Acid (HA) (Kablik, Monheit et al. 2009)

HA has excellent biocompatibility and affinity for water molecules, but it is a soluble polymer that is cleared rapidly when injected into normal skin. The two most common functional groups that can be modified in HA are the carboxylic acid and the hydroxyl group. Cross-linking strategies attempt to improve biomechanical properties while maintaining biocompatibility and biological activity. The hyaluronic acid contained in the products under discussion is cross-linked using 1,4 butanediol diglycidyl ether (BDDE). By BDDE-crosslinking, the hyaluronic acid chains are chemically stabilised through permanent epoxidic cross-links. After the cross-linking process, residual cross-linker is almost completely eliminated (specification: <1 ppm). Under basic conditions (pH>7) the epoxide groups of BDDE react with primary alcohols in the backbone of the hyaluronic acid forming ether bond connections and the epoxide groups are neutralised (figure 2-2).

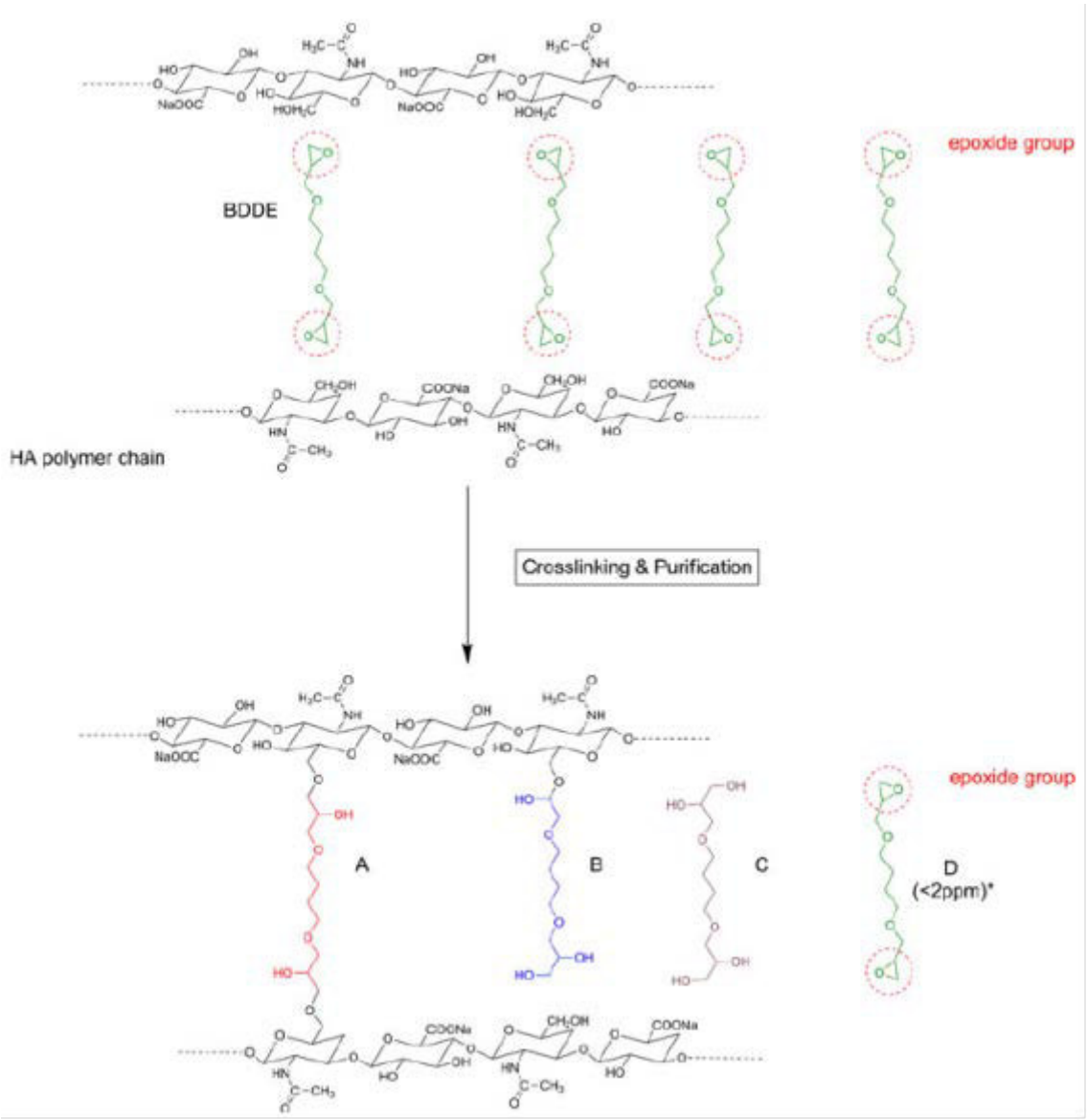

Figure 1: Schematic showing the cross-linking reaction of hyaluronic acid chains with BDDE. The epoxide groups in BDDE preferentially react with the primary hydroxyl groups in the hyaluronic acid backbone resulting in "fully reacted cross-linker" (A) or "pendant cross-linker" (B). BDDE that has not reacted with hyaluronic acid can be present in its hydrolized form (C) or its native form (D). By purification the amount of residual native BDDE in the product can be reduced to trace levels. Since this schematic demonstrates the crosslinking process with reference to the product Restylane® (Q-Med), residual amounts of unreacted BDDE are given as <2 ppm (De Boulle, Glogau et al. 2013).

When manufacturers convey the concentration of a filler, they are articulating the total amount of HA found in the filler, typically expressed in mg/mL (Figure 2-2). The total HA concentration consists of insoluble HA gel and soluble-free HA.

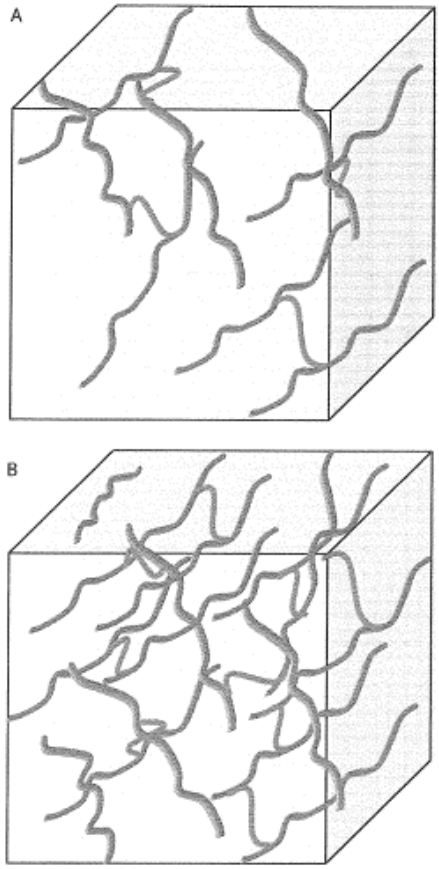

Figure 2-2: Concentration is a measure of the amount of HA in the gel. Given the same degree of cross-linking, low concentration will result in softer gels (A), whereas higher concentration gels result in stiffer gels (B) (Kablik, Monheit et al. 2009).

Mode of action

HYAcorp MLF1 / MLF2 / Genefill Contour is implanted into the subcutaneous and/or supraperiostal tissue to supplement the intercellular matrix and the intradermal tissue in order to restore lost anatomical structures. Its mechanism of action is based on the latest biotechnological developments in the production of injectable hyaluronic acid. The product is completely degraded over time.

Intended use

HYAcorp MLF1 / MLF2 / Genefill Contour is intended to be used as a means of restoring lost volume and contouring body surfaces. The depth of the injection can vary depending on the treatment site, the subcutaneous application and the supraperiostal application.

3. Intended therapeutic and/or diagnostic indications and claims

Application instructions and implantation technique

The areas to be treated must be marked before treatment begins. A local anaesthetic can be administered in order to carry out the implant as painlessly as possible. An antibiotic can be administered at the doctor's discretion to prevent infection. Remove the syringe from the blister pack, remove the cap covering the tip of the syringe and fit a suitable sterile needle to the Luer Lock port.

The implantation technique in terms of the depth of the injection and the amount administered can vary from case to case and according to the different degrees of augmentation required. The doctor must select the technique appropriate to the case in hand. Correct only up to 100 % of the volume of augmentation required. Do not carry out overcorrections. Explanations must be given to the patient before treatment is given about indications, warnings, intolerances as well as potential side effects and the results to be expected. The area to be treated must be carefully aseptically prepared before treatment.

Indication

- Volume restoration and contouring of

- Buttocks
- Calves

- Corrrection of concave deformities

Contouring the body with HYAcorp MLF1 / MLF2 / Genefill Contour ensures that the volume of the buttocks and other parts of the body is increased in a natural way. One of the uses of HYAcorp MLF1 / MLF2 / Genefill Contour is for contouring the cleavage, but it is also used to supplement cosmetic surgery procedures such as liposuction. The gel is injected deep into the skin and lifts the tissue in a natural way. The duration of the filling effect can vary and depends on the depth and the injection area. A greater augmentation of volume can be achieved with HYAcorp MLF2.

The results that can be achieved depend on the type of skin and on the changes requested. The treatment should be carried out only by doctors with knowledge and experience in the field of fat grafting or similar treatments.

Contraindications

The products must not be used in patients who:

- Have a tendency to hypertrophic and keloid scarring

- Have an intolerance towards gram-positive bacteria
- Are prone to active inflammatory or infectious processes
- Are suffering from acute or chronic skin diseases
- Are undergoinhg anti-coagulant therapy
- Have a known allergy against hyaluronic acid
- Are suffering from autoimmune diseases

No clinical data is available on the administration of the product during pregnancy or lactation or on its ad-ministration to adolescents under 18 years of age. Patients with multiple allergies should be excluded from treatment.

The use of HYAcorp MLF1 / MLF2 / Genefill Contour in the facial area is contraindicated. HYAcorp MLF1 / MLF2 / Genefill Contour is intended for subcutaneous and/or supraperiostal application only. The use of HYAcorp MLF1 / MLF2 / Genefill Contour for breast and genital augmentation is contraindicated.

Adverse Effects

As with any invasive procedure, treatment with HYAcorp MLF1 / MLF2 / Genefill Contour may also result in adverse effects. Treatment-related non-allergic reactions may occur such as itching, reddening, sensitivities and swelling at the puncture site, subcutaneous bleeding or haematoma as well as hardness or hypersensitivity reactions. In most cases these reactions occur immediately or up to one week after the injection and usually abate spontaneously within one or two weeks. Delayed side effects are very rare but can occur later after the injection. Known delayed side effects of dermal fillers are bacterial infections, biofilm formation, the formation of chronic inflammatory nodules, reactivation of herpes infections, migration of the filler material, skin necrosis, foreign body reactions and granuloma formation.

The injection technique can cause overcorrections or bluish discolorations (Tyndall effect). It is essential that side effects are diagnosed by an experienced doctor and appropriate treatment carried out and monitored. In order to minimise the risk of side effects from the outset, a thorough anamnesis must be taken by the doctor carrying out the treatment and the use of a sterile injection technique rigorously maintained.

Warnings and precautions

HYAcorp MLF1 / MLF2 / Genefill Contour must not be injected into blood vessels or intramuscularly as this could result in an occlusion of the vessels and an embolism.

HYAcorp MLF1 / MLF2 / Genefill Contour should not be injected into an area in which a permanent implant has been placed.

HYAcorp MLF1 / MLF2 / Genefill Contour should not be used on or in the vicinity of anatomical sites affected by an active skin disease, inflammation or associated conditions. The use of the product in areas that have already been treated with another augmentation solution is not recommended. The normal precautionary measures associated with intradermal injections must be observed.

HYAcorp MLF1 / MLF2 / Genefill Contour is intended for subcutaneous and/or supraperiostal injection. A technique and injection depth appropriate to the area treated must be chosen. To ensure the success of the treatment it is crucial that doctors using the product have the relevant expert knowledge and have undergone special technical training in injection techniques.

In common with all procedures of this type the implantation of HYAcorp MLF1 / MLF2 / Genefill Contour is associated with the inherent risk of an infection. A thorough anatomical knowledge of the treatment site is absolutely vital and special care must be exercised if areas are being treated in the direct vicinity of vulnerable structures such as nerves, vessels and the gut. The doctor carrying out the treatment should be thoroughly conversant with the patient's anamnesis. Suitable precautionary measures should be taken in the case of patients suffering from pre-existing diseases and guidance and explanations should be provided. Patients taking medication affecting blood clotting, such as aspirins or non-steroidal anti-inflammatory drugs, will experience, as is the case with any injection, increased bruising or increased bleeding at the injection site.

The area treated must not be exposed to excessive heat (sun, solarium, laser and IPL) or cold. Patients should refrain from sporting activities for a few days. The injection area should not be massaged in the days following the injection and not exposed to excessive pressure.

If the needle is clogged, replace it with a new one. Do not increase the pressure on the piston. Used syringes and needles should be treated as contaminated waste and must be disposed of in accordance with the generally accepted standards of medical practice.

The graduation on the syringe is intended as a guide for users based on the final volume. It does not perform any measuring function; it merely indicates the amount used in relation to the nominal volume of 10 ml. The doctor administering treatment should check visually and by touch that a sufficient amount of the material has been injected.

Classification

According to the Medical Device Directive 93/42/EEC, annex IX, rule 8, the products under discussion are classified as Class III Medical Devices.

4. Context of the evaluation and choice of clinical data types

To demonstrate the performance and safety of the products under discussion the principle of equivalence is chosen. The products under discussion are essentially similar to the products Macrolane™ VRF20 and Macrolane™ VRF30 (Q-Med, Uppsala, Sweden), which are established products on the market since several years. A summary of equivalence analysis is provided in tabular format in Attachment 2. Macrolane™ was developed and approved in Europe in 2006. The composition of the products can be considered as equivalent. Macrolane™ Volume Restoration Factor (VRF) gels, Macrolane™ VRF20 and Macrolane™ VRF30 are sterile, transparent gels of cross-linked hyaluronic acid of non-animal origin (20 mg/mL). The HA in Macrolane™ is generated by *Streptococcus*, and chemically cross-linked with 1,4-butanediol diglycidyl ether (BDDE). The products have a pH of 6.0 - 7.5. Macrolane™ VRF20 and VRF30 are designed for deep tissue implantation and differ with respect to the physical structure of the gel (Macrolane™ VRF20 is the thinner hylan gel). Macrolane™ VRF20 and VRF30 are supplied in plastic syringes with luer-lock. Each syringe is terminally moist heat sterilised in its packaging and packed in a paper carton. The products are for single use only (see IFU Macrolane™).

Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour are used for the same indications as Macrolane™ VRF20 and Macrolane™ VRF30. Macrolane™ VRF20 and Macrolane™ VRF30 are intended to be used for volume restoration and contouring of body surfaces. In general, deep subcutaneous administration is recommended. For both products sufficient tissue cover and support are important parameters to achieve a good esthetic treatment outcome. A minimum of 1 cm skin thickness, including subcutaneous fat, is usually required to attain good results. The choice between Macrolane™ VRF20 and Macrolane™ VRF30 is based on an assessment of tissue cover as determined by skin fold measures. Macrolane™ VRF30 is intended in areas where skin fold thickness is greater (see Instructions for Use of Macrolane™ VRF20 and Macrolane™ VRF30, (Heden, Sellman et al. 2009)).

Significant specification parameters of Macrolane™ VRF20 and Macrolane™ VRF30 and the products under discussion were analysed (see figure 4-1). It can be concluded that the products are essentially similar. Regarding physic-chemical parameters, Hyacorp MLF1/ Genefill Contour is equivalent to Macrolane™ VRF20 and Hyacorp MLF2 is equivalent to Macrolane™ VRF30. Thus, from a technical, biological, and clinical point of view, Macrolane™ VRF20 and Macrolane™ VRF30 can be considered to be equivalent to the products under discussion.

According to MEDDEV 2.7/1 rev3 evaluation of performance and safety of Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour based on published data regarding Macrolane™ VRF20 and Macrolane™ VRF30 is feasible.

Therefore, a thorough literature search in established databases is performed to demonstrate the performance and safety of Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour by taking products that are regarded as equivalent and the state-of-the-art of body contouring by filler materials into consideration.

In published literature, multiple studies are available addressing the evaluation of Macrolane™ for breast augmentation. Macrolane™ is no longer marketed for the breast indication due to an ongoing debate on issues with radiologic imaging for breast screening. Furthermore, the products under discussion are not indicated for breast augmentation. Thus, these publications are not considered as relevant in the present clinical evaluation. As Hyacorp MLF1 is identical with Genefill Contour, comparisons made between Hyacorp MLF1 and Macrolane VRF20 are also applicable.

Criterion	Hyacorp Body Contouring MLF 1 X18-3213/1	Macrolane VRF 20 Lot 12601	Evaluation
Route of administration	Syringe 10 ml	Syringe 10 ml	identical
Packing	Sterile in blister	Sterile in blister	identical
Sterilisation	Moist heat	Moist heat	identical
Osmolality	327 mosmol/kg	352 mosmol/kg	identical
Viscosity	19.000 mPas	18.500 mPas	identical
pH value	7.08	7.21	identical
Quantity of HA	20 mg/ml	20 mg/ml	identical
Source HA	fermentation	fermentation	identical
Cross linker	BDDE	BDDE	identical
BDDE residuals	< 0.001 mg/ml	< 0.001 mg/ml	Identical
Degree Crosslinking	9 %	11,9 %	identical
Particle size	311 µm	335 µm	identical
Elastic modulus G'	520 Pa (10 rad/s)	560 Pa (rad/s)	identical

Criterion	Hyacorp Body Contouring MLF 2 X5-3213/1	Macrolane VRF 30 Lot 12644	Evaluation
Route of administration	Syringe 10 ml	Syringe 10 ml	identical
Packing	Sterile in blister	Sterile in blister	identical
Sterilisation	Moist heat	Moist heat	identical
Osmolality	328 mosmol/kg	327 mosmol/kg	identical
Viscosity	16.000 mPas	15.500 mPas	identical
pH value	7.11	7.08	identical
Quantity of HA	20 mg/ml	20 mg/ml	identical
Source HA	fermentation	fermentation	identical
Cross linker	BDDE	BDDE	identical
BDDE residuals	< 0.001 mg/ml	< 0.001 mg/ml	Identical
Degree Crosslinking	18.4 %	17.9 %	identical
Particle size	336 µm	347 µm	identical
Elastic modulus G'	460 Pa (rad/s)	510 Pa (rad/s)	identical

Figure 4-1: Comparison of Hyacorp MLF1 with Macrolane™ VRF20 and Hyacorp MLF2 with Macrolane™ VRF30

5. Summary of the clinical data and appraisal

Following publications are regarded to contain sufficient information for a rational and objective assessment. All articles are relevant for the products under evaluation. The quality of the data is considered satisfactorily for articles taken into consideration. Protocol of the literature survey, corresponding results, and appraisal criteria are outlined in attachment 1.

The publications are categorized into the following sections: description of state-of-the-art, demonstration of performance and demonstration of safety.

For description of the current state-of-the-art mainly review articles are assessed. The performance of Macrolane™ VRF20 and Macrolane™ VRF30 is mostly gained from prospective trials providing sufficient information for a detailed assessment. Although representing a low level of clinical evidence, case reports were evaluated to investigate rare complications for the use of hyaluronic acid as dermal filler.

The final result of the appraisal of the literature is discussed below:

State-of-the-Art

Baumann, L. S., A. T. Shamban, et al. (2007). "Comparison of smooth-gel hyaluronic acid dermal fillers with cross-linked bovine collagen: a multicentre, double-masked, randomised, within-subject study." Dermatol Surg **33 Suppl 2**: S128-135.	A multicentre, double-masked, randomised, within subject study has been performed to compare the effectiveness and safety of these three HA dermal fillers (Juvéderm, Juvéderm Ultra, Juvéderm Ultra Plus) with those of a cross-linked bovine collagen filler for nasolabial fold (NLF) correction.	D2, A1, P1, R1
Butterwick, K. J., P. K. Nootheti, J. W. Hsu and M. P. Goldman (2007). "Autologous fat transfer: an in-depth look at varying concepts and techniques." Facial Plast Surg Clin North Am **15**(1): 99-111, viii.	The use of fat for volume restoration is becoming even more popular. This review article concerns newer techniques of Lipostructure, facial fat rebalancing, and fat autograft muscle injection (FAMI) that targeted to achieve true full-face three-dimensional rejuvenation.	P1 R1
Claoue, B. L. and P. Rabineau (2004). "The polyalkylimide gel: experience with Bio-Alcamid." Semin Cutan Med Surg **23**(4): 236-240.	Bio-Alcamid is a new nonbiodegradable substance which is easy to use and which allows one to create volume on both the body and the face. This substance is extractable even after several years. This allows more patients to use a nonbiodegradable substance for esthetic problems of lipoatrophy treatment or for posttraumatic or therapeutic atrophy of subcutaneous tissue.	P1 R2
Coleman, S. R. (2006). "Structural fat grafting: more than a permanent filler." Plast Reconstr Surg **118**(3 Suppl): 108s-120s.	In this article a physician reported on this experience with fat transfer. Exemplarily he discusses the outcome of three cases and and summarises procedural details.	P1 R2
De Meyere, B., S. Mir-Mir, J. Penas, C. C. Camenisch and P. Heden (2014). "Stabilized hyaluronic acid gel for volume restoration and contouring of the buttocks: 24-month efficacy and safety." Aesthetic Plast Surg **38**(2): 404-412.	This prospective, open-label, noncomparative, multicenter study (NCT01331408) performed in Belgium, Spain, and Sweden analyzed subjects 20 years of age or older seeking augmentation of the buttocks. The study was conducted in accordance with the Declaration of Helsinki and approved by the following independent ethics committees: Commissie voor medische ethiek, UZ, Gent; CEIC Fundacio´ Unio´ Catalana d'Hospitals,	D2 A1 P1 R2

	Barcelona; CEIC Hospital, Universitario La Princesa, Madrid; Regionala etikprovningsnamnden I Stockholm.	
Ellis, D. A. and L. Segall (2007). "Review of non-FDA-approved fillers." Facial Plast Surg Clin North Am **15**(2): 239-246, vii.	This article discusses some of the more popular soft tissue fillers, such as Restylane Fine Line, Restylane SQ, Perlane, Artecoll, Dermalive, Dermadeep, Bioalcamid, Bioplastique, Evolution, Outline, Argiform, and Aquamid, which are all available outside of the United States.	D2 A2 P1 R2
Gold, M. (2009). "The science and art of hyaluronic acid dermal filler use in esthetic applications." J Cosmet Dermatol **8**(4): 301-307.	This publication has to be regarded as a review article; reflecting the state-of-the-art mainly in the years from 2004 to 2008; consensus statements and randomised trials are discussed as well. Especially the dermal fillers Juvéderm and Restylane/Perlane are discussed; application areas are upper, mid, and lower face.	A1, P2, R1
Guyuron, B. and R. K. Majzoub (2007). "Facial augmentation with core fat graft: a preliminary report." Plast Reconstr Surg **120**(1): 295-302.	A total of 21 patients have undergone facial augmentation with the core fat graft technique over a period of 16 months. Included in this report are the outcomes of augmentation of 26 sites on 16 patients who are at least 6 months postoperative.	P1 R2
Heden, P., G. Sellman, M. von Wachenfeldt, M. Olenius and D. Fagrell (2009). "Body shaping and volume restoration: the role of hyaluronic acid." Aesthetic Plast Surg **33**(3): 274-282.	This review focuses on the use of hyaluronic acid for body contouring and breast augmentation. It also briefly discusses the range of alternative treatment options for body reshaping. Furthermore, the authors report on their prospective pilot study using Macrolane for buttock contouring.	D2 A1 P1 R1
Klein, A. W. (2006). "Soft tissue augmentation 2006: filler fantasy." Dermatol Ther **19**(3): 129-133.	This review articles focuses on various injectable filler agents available. Requirements on soft tissue fillers are discussed.	R1
Lupo, M. P. (2006). "Hyaluronic acid fillers in facial rejuvenation." Semin Cutan Med Surg **25**(3): 122-126.	Review article. This publication represents an overview for hyaluronic acid as a dermal filler. The advantage of hyaluronic acid compared other dermal fillers like collagen is discussed. The article represents and summarizes publications from 1986 to 2005. Restylane and other sorts of hyaluronic acid (avian origin) are described.	A1, P1, R2
Matarasso, S. L., J. D. Carruthers, et al. (2006). "Consensus recommendations for soft-tissue augmentation with nonanimal stabilised hyaluronic acid (Restylane)." Plast Reconstr Surg	Review article and consensus statement, mainly focusing on the product Restylane. Besides products, procedural aspects were discussed in detail. The time period from 2000 to 2005 is covered.	D2, A1, P2, R2

117(3 Suppl): 3S-34S; discussion 35S-43S.		
Moseley, T. A., M. Zhu and M. H. Hedrick (2006). "Adipose-derived stem and progenitor cells as fillers in plastic and reconstructive surgery." Plast Reconstr Surg **118**(3 Suppl): 121s-128s.	In this article current knowledge on adipose derived stem stells for body contouring is summarised. Regenerative cell-based strategies such as those encompassing the use of stem cells hold tremendous promise for augmentation of the soft-tissue space.	R1
Newman, J. (2009). "Review of soft tissue augmentation in the face." Clin Cosmet Investig Dermatol **2**: 141-150.	Review article covering the time period from 2000 to 2008. This article described the current options of tissue augmentation; pro and cons are discussed in an objective manner. In addition absorbable fillers, non-absorbable material, and methods using autologous material are discussed.	D2, A1, P1, R2
Ramires, P. A., M. A. Miccoli, E. Panzarini, L. Dini and C. Protopapa (2005). "In vitro and in vivo biocompatibility evaluation of a polyalkylimide hydrogel for soft tissue augmentation." J Biomed Mater Res B Appl Biomater **72**(2): 230-238.	All of the reported studies are focused on the biocompatibility evaluation of a polyacrylic hydrogel containing alkylimide-amide groups and pyrogen free water (96%) (Bio-Alcamid_) by means of the *in vitro* cytotoxicity and mutagenicity assays and the *in vivo* skin irritation, sensitization test, and subcutaneous implant.	R1
Rohrich, R. J., A. Ghavami, et al. (2007). "The role of hyaluronic acid fillers (Restylane) in facial cosmetic surgery: review and technical considerations." Plast Reconstr Surg **120**(6 Suppl): 41S-54S.	Review article. The product Restylane is described in detail; procedural aspects are discussed as well. Main focus of this article is the facial rejuvenation. The performance of Restylane is shown. Possible complications and there occurrence are discussed.	A1, P2, R1
Smith, K. C. (2008). "Reversible vs. nonreversible fillers in facial aesthetics: concerns and considerations." Dermatol Online J **14**(8): 3.	Review article dealing with hyaluronic acid as dermal filler in general. History, development and alternatives in tissue augmentation is presented. The major and unique advantage of HA fillers, the reversion by hyaluronidase is outlined.	A2, P1, R2
Tezel, A. and G. H. Fredrickson (2008). "The science of hyaluronic acid dermal fillers." J Cosmet Laser Ther **10**(1): 35-42.	Several chemical and physical characteristics of hyaluronic acid and their influence on final product performance are described. The equilibrium of longevity and purity, safety, and ease of administration is discussed in detail.	D2 A1 P1 R1

Performance

Camenisch, C. C., M. Tengvar and P. Heden (2013). "Macrolane for volume restoration and contouring of the buttocks: magnetic resonance imaging study on localization and degradation." Plast Reconstr Surg **132**(4): 522e-529e.	This was a prospective, open-label, noncomparative study performed using subjects aged 20 years or older in Stockholm, Sweden. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local independent ethics committee (Regionala etikprövningsnämnden i Stockholm).	D2 A1 P1 R2
Cerqua, S. and F. Angelucci (2013). "Macrolane (large particle biphasic hyaluronic acid) filler injection for correction of defect contour after liposuction." J Cosmet Laser Ther **15**(4): 228-230.	In this study, the authors investigated the effectiveness, maintenance, and safety of Macrolane as a "non-surgical" treatment to correct skin depression after liposuction. Twelve female patients were included. Macrolane was injected at a subdermal superficial plane using an intramuscular or spinal needle.	D2 A1 P1 R2
De Meyere, B., S. Mir-Mir, J. Penas, C. C. Camenisch and P. Heden (2014). "Stabilized hyaluronic acid gel for volume restoration and contouring of the buttocks: 24-month efficacy and safety." Aesthetic Plast Surg **38**(2): 404-412.	This prospective, open-label, noncomparative, multicenter study (NCT01331408) performed in Belgium, Spain, and Sweden analyzed subjects 20 years of age or older seeking augmentation of the buttocks. The study was conducted in accordance with the Declaration of Helsinki and approved by the following independent ethics committees: Commissie voor medische ethiek, UZ, Gent; CEIC Fundacio´ Unio´ Catalana d'Hospitals, Barcelona; CEIC Hospital, Universitario La Princesa, Madrid; Regionala etikprovningsnamnden I Stockholm.	D2 A1 P1 R2
Hartmann, V., F. Bachmann, M. Plaschke, T. Gottermeier, A. Nast and B. Rzany (2010). "Hand augmentation with stabilized hyaluronic acid (Macrolane VRF20 and Restylane Vital, Restylane Vital Light)." J Dtsch Dermatol Ges **8**(1): 41-44.	Volume augmentation of the back of the hand is a new technique which is not yet often employed. In this small-scale clinical experiment, the treatment of two patients was described who received hyaluronic acid products produced by Q-Med (Macrolane™ VRF20, Restylane® Vital and Vital Light). The injections of Macrolane™ VRF 20 were done by feathering technique using a long and blunt 18 gauge canula while Restylane® was injected by tunneling or tenting technique with a 30 gauge needle.	D2, A1, P1, R2
Heden, P., G. Sellman, M. von Wachenfeldt, M. Olenius and D. Fagrell (2009). "Body shaping and volume restoration: the role of hyaluronic acid." Aesthetic Plast Surg **33**(3): 274-282.	This review focuses on the use of hyaluronic acid for body contouring and breast augmentation. It also briefly discusses the range of alternative treatment options for body reshaping. Furthermore, the authors report on their prospective pilot study using Macrolane for buttock contouring.	D2 A1 P1 R1
Sinna, R., D. Perignon, N. Assaf and P. Berna (2012). "Use of	The authors report on the use of Macrolane for the treatment of mild pectus excavatum. However they	D2 A2

Macrolane to treat pectus excavatum." Ann Thorac Surg **93**(1): e17-18.	focus on technical details and procedural aspects, and no details on the outcome are provided.	P2 R1

Safety

Andre, P., N. J. Lowe, et al. (2005). "Adverse reactions to dermal fillers: a review of European experiences." J Cosmet Laser Ther **7**(3-4): 171-176.	This review article summarised publications and case reports. It described the clinical aspects of adverse reactions following injections of dermal filler (absorbable, non biodegradable and permanent) And provides valid information on safety of dermal fillers	D2 A2 P1 R1
Beasley, K.L. (2009). "Hyaluronic Acid Fillers: A comprehensive Review". Facial Plast Surg. 25:86-94.	Since 85 % of all dermal filler procedures occurred with a hyaluronic acid derivate this review summarised the composition,, specific differences and pivotal clinical studies of all the hyaluronic acid fillers currently available in the US.	D2, A1, P2, R1
Chaput, B., H. Eburdery, C. Crouzet, J. L. Grolleau, J. P. Chavoin and I. Garrido (2012). "[Macrolane(R): A severe case of calf cellulitis after modeling injection]." Ann Chir Plast Esthet **57**(1): 83-86.	This is a case report on severe cellulitis after Macrolane treatment in a 61-year old patient.	D2 A1 P2 R2
De Meyere, B., S. Mir-Mir, J. Penas, C. C. Camenisch and P. Heden (2014). "Stabilized hyaluronic acid gel for volume restoration and contouring of the buttocks: 24-month efficacy and safety." Aesthetic Plast Surg **38**(2): 404-412.	This prospective, open-label, noncomparative, multicenter study (NCT01331408) performed in Belgium, Spain, and Sweden analyzed subjects 20 years of age or older seeking augmentation of the buttocks. The study was conducted in accordance with the Declaration of Helsinki and approved by the following independent ethics committees: Commissie voor medische ethiek, UZ, Gent; CEIC Fundacio´ Unio´ Catalana d'Hospitals, Barcelona; CEIC Hospital, Universitario La Princesa, Madrid; Regionala etikprovningsnamnden I Stockholm.	D2 A1 P1 R2
Gilbert, E., A. Hui et al. (2012)."The basic science of dermal fillers: past and present Part II: adverse effects." J Drugs Dermatol **11**(9): 1069-1077.	Part I of this article reviews the basic science and evolution of both historical and contemporary dermal fillers; Part II examines their adverse effects.	D2, A1, P2, R2
Hartmann, V., F. Bachmann, M. Plaschke, T. Gottermeier, A. Nast	Volume augmentation of the back of the hand is a new technique which is not yet often employed.	D2, A1,

and B. Rzany (2010). "Hand augmentation with stabilized hyaluronic acid (Macrolane VRF20 and Restylane Vital, Restylane Vital Light)." J Dtsch Dermatol Ges **8**(1): 41-44.	In this small-scale clinical experiment, the treatment of two patients was described who received hyaluronic acid products produced by Q-Med (Macrolane™ VRF20, Restylane® Vital and Vital Light). The injections of Macrolane™ VRF 20 were done by feathering technique using a long and blunt 18 gauge canula while Restylane® was injected by tunneling or tenting technique with a 30 gauge needle.	P1, R2
Heden, P., G. Sellman, M. von Wachenfeldt, M. Olenius and D. Fagrell (2009). "Body shaping and volume restoration: the role of hyaluronic acid." Aesthetic Plast Surg **33**(3): 274-282.	This review focuses on the use of hyaluronic acid for body contouring and breast augmentation. It also briefly discusses the range of alternative treatment options for body reshaping. Furthermore, the authors report on their prospective pilot study using Macrolane for buttock contouring.	D2 A1 P1 R1
Hirsch, R. J. and M. Stier (2008). "Complications of soft tissue augmentation." J Drugs Dermatol **7**(9): 841-845.	This article describes a range of complications resulting from dermal filler injections, reviews key case studies, and discusses possible treatment options for adverse effects. Mainly publications from 2000 to 2008 were discussed.	D2 A2 P1 R1
Matarasso, S. L., J. D. Carruthers, et al. (2006). "Consensus recommendations for soft-tissue augmentation with nonanimal stabilised hyaluronic acid (Restylane)." Plast Reconstr Surg **117**(3 Suppl): 3S-34S; discussion 35S-43S.	Review article and consensus statement, mainly focusing on the product Restylane. Besides products, procedural aspects were discussed in detail. The time period from 2000 to 2005 is covered.	D2, A1, P2, R2
Newman, J. (2009). "Review of soft tissue augmentation in the face." Clin Cosmet Investig Dermatol **2**: 141-150.	Review article covering the time period from 2000 to 2008. This article described the current options of tissue augmentation; pro and cons are discussed in an objective manner. In addition absorbable fillers, non-absorbable material, and methods using autologous material are discussed.	D2, A1, P1, R2
Price, R.D, et al (2007). "Hyaluronic acid: the science and clinical evidence". J Plast Reconstr Aesthet Surg. **60**, 1110-1119	This review represents an overview about the scientific evidence of HA used in different fields such as skin regeneration, wound healing and cosmetic surgery.	D2, A2, P2, R1
Winslow, C. P. (2009). "The management of dermal filler complications." Facial Plast Surg **25**(2): 124-128.	The purpose of this article is to review the most commonly encountered complications and management thereof. Literature published between 2006 and 2008 are taken into consideration.	D2, A2, P2, R1

6. Data analysis

6.1 State-of-the-Art

As an increasing number of patients seek esthetic improvement through minimally invasive procedures, interest in soft tissue augmentation and filling agents is at an all-time high (Klein 2006). The American Society of Plastic Surgeons reported on 13.48 millions of conducted aesthetic minimally-invasive procedures in the U.S. in 2013 (in contrast to 1.67 millions of aesthetic surgical procedures). About 2.24 millions of soft tissue filler injections were administered to patients, of which 1.68 millions were hyaluronic acid injections (numerous different products) (http://www.plasticsurgery.org/news/plastic-surgery-statistics/2013.html).

The skilled plastic surgeon has a wide range of techniques and products available to create volume in the body. Although the type of defect in question very often limits the selection of interventions available, it is a reasonable assumption that where possible, patients prefer minimally invasive procedures over more drastic interventions. This assertion is supported by the remarkable growth in the number of minimally invasive procedures performed. Although the data do not demonstrate that minimally invasive procedures are replacing surgical treatments, the greater availability and choice of procedures appear to have stimulated increased demand (Heden, Sellman et al. 2009).

Minimally invasive procedures offer several benefits. They can be performed using local anesthesia, thus reducing the risk of complications arising from general anaesthesia, and do not require hospitalization. Because the area of open tissue exposed is limited, the risk of serious infections is consequently reduced. Given that many patients seek augmentation for purely cosmetic purposes, avoiding the hospital environment is clearly desirable. Because the extent of trauma is less than with invasive procedures, recovery times tend to be shorter, and the patient can return to his or her normal routine far more quickly. There also may be less requirement for pain management, and patients usually can cope using over-thecounter remedies (Heden, Sellman et al. 2009).

Body contouring is performed for both medical and aesthetic reasons. For example, in De Meyere et al, the main reasons why people request buttock augmentation are summarised: to regain shape lost by weight loss or aging, to increase attractiveness and to correct human immunodeficiency virus (HIV)-associated lipoatrophy (De Meyere, Mir-Mir et al. 2014).

The available treatment options include permanent, semi-permanent, and non-permanent solutions. The ideal volume enhancer agent is biocompatible, predictable, adjustable to the anatomy of the patient, long-lasting, reversible, and natural in appearance. However, no filler material possesses all of these characteristics. The different materials that can be used for body contouring – with focus on hyaluronic acid – are presented in the following.

6.1.1 Hyaluronic acid as filler agent

Hyaluronic acid (HA)-based gels are now the gold standard in dermal fillers, with more cosmetic procedures in the United States using these fillers than all other fillers combined. The widespread acceptance of HA fillers is testament to their biocompatibility (unlike protein-based fillers, they are composed of polysaccharides that exhibit no species specificity), the stability of their cross-linked HA *in vivo* (which promotes longevity of clinical improvement), and their good record of safety and effectiveness in other countries where they have been in use for many years (Baumann, Shamban et al. 2007).

Hyaluronic acid, or hyaluronan, is a glycosaminoglycan that consists of regularly repeating non-sulfated disaccharide units of glucuronic acid and N-acetylglucosamine. Hyaluronan is a naturally occurring biopolymer that exhibits no species or tissue specificity. It is an essential component of the extracellular matrix of all adult animal tissues and is especially abundant in early embryos. Hyaluronan normally exists in tissues as a free polymer of linked disaccharide units and is highly negatively charged. However, in some tissues, such as cartilage and bone, hyaluronan is bound to large glycoprotein structures or specific cell receptors. In healthy tissues, the average molecular weight of hyaluronan is 5 to 10 million with up to 25,000 disaccharide units, and the average adult concentration is 200 mg/kg (0.02 %) (Matarasso, Carruthers et al. 2006).

A series of chemical modification and processing steps must be applied to HA to develop viable formulations for use as dermal fillers. The raw HA polymer used to produce dermal fillers is usually supplied to the manufacturer in dry powder form. In order to overcome the lack of persistence of uncross-linked HA, dermal filler manufacturers use cross-linkers. The cross-linkers bind HA polymer chains to each other, creating a polymer 'network' and transforming the viscous liquid into a gel. The resulting HA gel acts as a single unit, imposing a physical and chemical barrier to enzymatic and free radical breakdown (Tezel and Fredrickson 2008).

Cross-linked derivatives have been shown to be well tolerated when injected into locations such as the skin and vocal folds. The use of HA is particularly attractive for soft-tissue augmentation, because it is hydrophilic and a normal extracellular component of skin. Factors that impact HA persistence include HA concentration, percentage of cross-linkage, type of cross-linking, its fluid retention (i.e., water binding capacity), and injection technique. The two most important factors are the percentage of cross-linking and the water binding capability of the hyaluronic gel. When uncross-linked HA is added to water it produces a highly viscous liquid that would only last a few days in human skin. Manufacturers use various agents to cross-link the HA. As a result, the final proportion of cross-linked HA and the degree of cross-linking impact the physical characteristic of the final product (Newman 2009).

Almost all HA fillers on the world market use 1 of 3 basic cross-linking chemistries. Of these 3, butanediol diglycidyl ether (BDDE) has by far the longest track record (about 20 years as of July 2008), and the greatest amount of clinical experience (many millions of patients treated worldwide including North America) (Smith 2008).

One very important characteristic of HA products is the ability of clinicians to break down the cross-linking of each product with the use of an enzyme known as hyaluronidase. This enzyme

breaks the cross-links by hydrolysis of the glucosamine and glucornic acid moiety. This result in the breakage of the cross-links and the three-dimensional structure of HA becomes absorbed within hours by the surrounding interstitial fluid. One note of caution is the possibility of allergic reaction with purified bovine testicular hyaluronidase or with preparations that contain metabisulfite (Newman 2009).

In general clinical trials have documented the overwhelming safety profile of all forms of HA. Transient and self-limiting redness and swelling are common following injections of HA and this is due to the hydrophilic nature of HA. Pain associated with injection may be managed by the use of both topical and injected anesthetic agents. Despite adequate anaesthesia, patients can expect tenderness for 1 to 2 days after injection (Lupo 2006).

Potential adverse reactions are minimal and are mainly injection-related and self-resolving. These include local bruising, purpura, erythema, and tenderness, itching, and swelling. A major adverse event that has been reported is hypersensitivity, but true immunoglobulin G- and E-mediated reactions are rare (Rohrich, Ghavami et al. 2007).

Although no treatment is entirely without risk, the side effect profiles of HAs and other dermal fillers have been reviewed extensively. HAs in general have demonstrated excellent benefit–risk profiles. Serious adverse events are rare, and most reactions are transient, injection-site related, and mild to moderate in severity (Gold 2009).

6.1.2 Other treatment options for body contouring

Fat transfer

With the advent of liposuction, plastic surgeons were afforded a valuable by-product, namely semiliquid fat, that could be implanted with relative ease using a needle or small cannula. Autologous fat transfer is intuitively appealing. The material is completely biocompatible, requires no pretesting, and usually is available in ample quantities (Coleman 2006). Implanted fat can be removed if required yet also has the potential to be permanent. Because the ability to remove fat from sites of excess and to implant it into sites of deficiency allows the body to be sculpted, fat grafting has become increasingly popular. The prospective use of adipose tissue stem cells in tissue rejuvenation after implantation also has been investigated (Moseley, Zhu et al. 2006). However, fat grafting is not without its disadvantages. Infection is always possible with surgical procedures, and damage to local nerves, muscles, glands, and blood vessels is a possibility during harvesting. Compared with allogeneous injectable products, the procedure is time consuming and expensive, with unpredictable efficacy, and often is associated with pronounced swelling of the recipient tissues. A number of studies also have reported disappointinglong-term survival rates for implanted fat, relatively low rates for long-term patient satisfaction, and excessive growth of the transplanted fat (Heden, Sellman et al. 2009). Furthermore, fundamental questions remain regarding the optimal harvesting site, processing technique, and most effective injection technique (Butterwick, Nootheti et al. 2007). Additionally, segmental fat transfer is possible. It requires donor- and recipient-site incisions and has the potential for scar visibility (Guyuron and Majzoub 2007).

Flap surgery

Flap surgery can be used to create substantial volume for areas of deficiency, usually those arising from trauma (injury or surgery), tumor removal, and burns. For example, in breast reconstruction, the latissimus dorsi muscle flap can be used without significant loss of function. It can be moved into the breast defect while still attached to its blood supply under the axilla. Flap surgery often involves complex procedures associated with donor-site morbidity and considerable scarring, which are highly significant drawbacks to such surgery. It is therefore not an appropriate option for patients considering a procedure to create modest amounts of volume for purely aesthetic improvement (Heden, Sellman et al. 2009).

Silicone implants

The placement of silicone implants can provide long-lasting correction and substantial volume, hence their widespread use for breast augmentation. However, as with any invasive procedure, complications after implant surgery are not uncommon. It also is important to note that irrespective of how the implant is constructed or the hardness of the gel used, reoperation can be expected in a relatively large proportion of cases. Recent reports indicate that the risk of complications within the 3-year period after implantation is as high as 50% with some silicone implants. Generally, silicone implants are not useful for correcting smaller concavities such as irregularities after liposuction or small scars (Heden, Sellman et al. 2009).

Injectable silicone

Use of medical grade silicone to repair complicated retinal detachments is approved by the regulatory authorities in both the United States and the European Union. Its off-label use for cosmetic purposes also has been explored. Injection of silicone elicits a chronic inflammatory reaction, with giant cell formation and encapsulation of the injected product in fibrous tissue, thereby creating volume. The use of injectable silicone has been hampered by adverse effects such as infection, palpable nodule formation, granuloma formation, migration, and silicone embolism (Ellis and Segall 2007). However, its proponents claim that it is easy to use, long-lasting, and low in cost, and that high rates of complications usually are associated with the improper use of industrial grade silicone injected by unlicensed or unskilled practitioners. Nevertheless, reports in the peer-reviewed literature to support its use for correction of large-scale volume deficiencies in the body are lacking (Heden, Sellman et al. 2009).

Polyalkylimide gel

Polyalkylimide gel (Bio-Alcamid; Polymekon Laboratories, Italy) received a CE mark in 2001 for use to create volume in both the face and body for cosmetic purposes. A review article stated that the product is biocompatible, is easy to inject and remove, does not migrate, and can be used for correction of slight to very serious aesthetic defects (Ramires, Miccoli et al. 2005).

The gel has been used to repair muscular defects after trauma, to augment the buttocks, and to correct postpoliomyelitis amyotrophy of the calves and pectus excavatum as well as irregularities after liposculpture and scar depressions (Claoue and Rabineau 2004).

However, given the potential permanency of the gel and various reports of serious complications such as granuloma formation, long-term studies of the agent are required to confirm its safety and efficacy (Heden, Sellman et al. 2009).

Polyacrylamide gel

Polyacrylamide hydrogel is a nonresorbable sterile ‘‘watery’’ injectable gel (Aquamid; Contura, Soeborg, Denmark). Aquamid received its CE mark for soft tissue facial augmentation and corrections in 2001, which was extended in 2003 to include soft tissue corrections of the body. High rates of patient satisfaction have been reported for Aquamid treatment of facial contour deformities or soft tissue deficiencies caused by aging, acne, trauma, and surgery. However, no studies on the safety and efficacy of this treatment for body contour deformities have been published (Heden, Sellman et al. 2009).

6.2 Performance

6.2.1 Performance of Macrolane™

A nonrandomised, open-label pilot study was conducted recently to explore the efficacy, duration of effect, and tolerability of the initial Macrolane formulation for recontouring body deformities of different etiologies (irregularities after liposuction and scars arising from trauma or surgery). Macrolane™ was injected supraperiostally and/or into the subcutaneous fatty tissue, then spread into the area to be augmented. Patients initially were treated with Macrolane™ (<20 ml), with an optional ‘‘touchup’’ treatment given 4 weeks later. Efficacy was assessed independently by patients and investigators at 4 weeks, then 3, 6, 9, and 12 months after the last treatment using the Global Aesthetic Improvement Scale (GAIS). The proportion of patients rated as improved (somewhat improved, moderately improved, or very much improved) was calculated using the ‘‘intention-to-treat’’ approach in an ‘‘observed case’’ manner (i.e., no imputations were made for missing data). Of the 56 patients recruited, 46 completed the study. The patients initially received a mean Macrolane™ volume of 16.6 ± 8.5 ml. ‘‘Touch-up’’ treatment was performed for 16 of the 56 patients, who received a mean gel volume of 14.7 ± 4.9 ml. The proportions of improved patients, as assessed by the study investigators, were 87% at 4 weeks, then 85% at 3 months, 69% at 6 months, 75% at 9 months, and 52% at 12 months. The corresponding rates, as assessed by the patients, were 81%, 80%, 69%, 70%, and 57% (Heden, Sellman et al. 2009).

In a prospective, open-label noncomparative, multicenter study performed in Belgium, Spain, and Sweden subjects seeking augmentation of the buttocks were analysed. A maximum of 400 mL of stabilised HAgel (Macrolane™ VRF30) per subject was injected into the deep subcutaneous fatty tissue supramuscularly through a 5-mm incision created using a no. 15 scalpel blade. The position of the incision was determined at the discretion of the investigators. The subjects received local anesthesia in the injection area. The subjects were followed up for safety and efficacy 1 month (3–6 weeks) and then 6, 12, 18, and 24 months after treatment. An optional touch-up treatment could be performed within 8 weeks after the initial treatment. In this study, 61 subjects were treated with Macrolane™ VRF30 injections in the buttocks, and 17

subjects received touch-up treatment within 8 weeks after the initial treatment. Of the 61 subjects, 50 completed the 24-month follow-up period. Nine were lost to follow-up evaluation. One subject moved, and one subject withdrew from the study due to removal of the gel because of its complete dislocation (discussed in section 6.3). The patients (57 females, 4 males) had a mean age of 41.3 years (range 20.1-64.5) and were mainly Caucasians (88.5%). In a substudy of eight patients MRI assessment was done: 100, 56, 36, and 24 % of the injected hylan gel remained in the buttocks per subject respectively 1–5 days, and then 6, 12, and 24 months after treatment. Concerning all treated patients, According to Global Aesthetic Improvement Scale (GAIS) assessment, 6 months after treatment, buttock appearance was rated as improved or better (i.e., ‘‘improved,’’ ‘‘much improved,’’ or ‘‘very much improved’’) in 80 % of the subjects as assessed by the subjects themselves (95 % CI 68–90 %), and in 91 % of the subjects as assessed by the investigators. At 1 year after treatment, buttock appearance was assessed as improved or better in the majority of subjects by both the subjects themselves (68 % improved subjects) and the investigators (62 % improved subjects). The improvement rates reported by subjects still were 42 % at 18 months and 40 % at 24 months. Investigator assessments of improvement rates were 35 % at 18 months and 30 % at 24 months. Before entering the study, approximately half of the subjects were dissatisfied with their buttocks in general: 75 % with the firmness, 61 % with the size, and 64 % with the shape. After treatment, the subjects' satisfaction with the general appearance, shape, size, and firmness of their buttocks increased and remained higher throughout the study period than before treatment. For example, general satisfaction rose from below 20 % before treatment to above 70 % 1 month after treatment, then declined thereafter to about 40 % of subjects being satisfied 12 months after treatment. Even after 24 months, at least 33 % of subjects still reported general satisfaction with their buttocks. Furthermore, in this study, outcomes were correlated with the patient´s body mass index (BMI). The results of the current study suggest that subjects with a low BMI are not suitable candidates for buttock enhancement because they have a higher risk of visibility or palpability of the gel. However, in summary, Macrolane^{TM} VRF30 can be regarded as effective in this clinical trial. Although the substance degrades over time, a good proportion of subjects still rated their buttocks as improved and expressed satisfaction with the results 24 months after treatment (De Meyere, Mir-Mir et al. 2014).

More detailed information on the MRI assessment in the eight patients can be found in Camenisch et al. Magnetic resonance imaging was performed on the subjects in the prone position 1 to 5 days, 6 months (±14 days), 12 months (±28 days), and 24 months (±28 days) after treatment. Posttreatment scans 1 to 5 days after injection demonstrated that more than 60 percent of the gel was located in the deep subcutaneous fat in six of the subjects. The remaining gel was generally located intramuscularly. By 6 and 12 months after treatment, seven and six subjects, respectively, had more than 60 percent of the gel located in the subcutaneous fat. After 24 months, three of five subjects had more than 60 percent of the gel located in the subcutaneous fat, whereas over time, gel placed intramuscularly tended to degrade more than gel placed in the subcutaneous fat. At 6, 12, and 24 months after treatment, respectively, means of 56 percent (183.5 ml), 36 percent (118.7 ml), and 24 percent (86.7 ml) of the gel remained in the buttocks, although the degradation rate was highly variable between subjects. The degradation rate between buttocks was similar, allowing for an even appearance at all time points. At the 6-month visit, parts of hyaluronic acid gel implant had changed position in five subjects (62.5 percent) since the initial examination. Changes in position included local

displacement of the product in the superior, medial, and/or lateral direction; and coalescence of product to form fewer but larger deposits. There were no further changes in the position of the gel at 12 and 24 months after initial treatment. No subject experienced displacement of the product outside of the buttock area. These data demonstrate that Macrolane™ VRF30 degraded as expected in the buttocks and there was minimal displacement of the gel (Camenisch, Tengvar et al. 2013).

Macrolane™ VRF20 has been investigated for hand augmentation in comparison to the dermal fillers Restylane® Vital and Restylane® Vital light (both Q-Med, Uppsala, Sweden). The comparator products consist of non-crosslinked hyaluronic acid. In this small-scale experiment, one patient received Macrolane™ VRF20 into the subcutis of the back of both hands. After injection the material was modeled by massage. At the end of the treatment, small irregularities were corrected with Restylane® Vital light. A total of 10 mL Macrolane™ VRF20 and 3 mL Restylane® Vital Light were distributed to both hands. Ten days after treatment we observed a very good improvement of appearance with substantial reduction of visibility of the veins and tendons as well as symmetrically filled interphalangeal spaces. At a visit after 3 months continued distinctly improved appearance was seen. In a second patient, more superficial injection were performed with Restylane® Vital and Restylane® Vital light. A total of 1 mL each Restylane® Vital and Vital Light were used on the back of the left hand. Here, too, after the injection the material was mildly massaged in. After 10 days a distinct improvement that was still present after 3 months was observed. In both cases patients were highly satisfied (Hartmann, Bachmann et al. 2010). Although the administration of Macrolane™ VRF20 for hand augmentation is a case report only, there are clear indications that the performance of Macrolane™ VRF20 in hand augmentation is adequate.

In a minority of patients undergoing liposuction, superficial irregularities (or skin depression) in the operated area may occur. In the prospective, monocentric study of Cerqua et al, the authors investigated the effectiveness, maintenance, and safety of Macrolane™ as a "non-surgical" treatment to correct skin depression after liposuction. Twelve female patients were included. Macrolane™ (10 to 12 mL) was injected at a subdermal superficial plane using an intramuscular or spinal needle. In all patients, Macrolane™ was successful in correcting skin depression at 4, 6, and 8 months after treatment. At 8 months post-injection, a persistence of correction of 60-70% was still present in 11 of 12 of the patients. In conclusion, Macrolane™ filler injections are a predictable and long-lasting non-surgical procedure to fill contour defects that arise after liposuction, and represent a good option for patients who refuse to undergo an additional surgery to fill the arisen skin depressions (Cerqua and Angelucci 2013).

Moreover Sinna et al reported on the feasibility of Macrolane™ injections in correction of pectus excavatum. However, in this study, no information on study design, number of patients included, or means of monitoring are provided (Sinna, Perignon et al. 2012).

6.3 Safety

6.3.1 Hyaluronic acid

Since HA occurs naturally in the human body, the risk of allergic reactions is very low and thus, the manufacturers suggest that there is no need for skin testing before. The differences in chain length molecular weight do not appear to have any clinical significance. Adverse effects related to HA injection are most commonly localized, immediate, and non-allergic, and include pain, edema, and ecchymoses. Additional side effects to consider are an angioedema-like swelling and hypersensitivity as well as the rare rapidly developing bacterial infection acquired transdermally while injecting (Gilbert, Hui et al. 2012).

In fact, there is a very small amount of proteins which can lead to some hypersensitivity reactions. Anti-HA antibodies have been demonstrated but the clinical significance is not exactly known. A retrospective European survey has evaluated the risk of important adverse reactions with the HA from Q-Med from 1997 to 2001. A total of 4,320 patients were evaluated and 12,344 syringes were injected. From 1997 to 2001, 34 cases of hypersensitivity are reported: 16 cases of immediate hypersensitivity and 18 cases of delayed reactions. Global risk is 0.8 %. Since 2000, the load of proteins of the Q-Med product has decreased, and the incidence of hypersensitivity reactions has become around 0.6 %. As 50 % of theses reactions are immediate and resolved within less than three weeks, the risk of transient delayed reactions was around 0.3 % with the old formulations. These are now significantly less frequent (less than 1 in 2000 treatments) with the current Q-Med products. These remain the most used products in the UK and are very predictable. Sterile abscess and lividoid pattern after intra vascular injection has been reported. No systemic reactions have been reported. Non-animal HA from the Q-Med company does not need skin testing. In cases of ‘‘inflammatory’’ reactions, the histological aspects can be either a moderate lymphocytic infiltrate with some plasma cells in the dermis and the hypodermis or a lymphocytic infiltrate with macrophages and presence of foreign body giant cells (Andre, Lowe et al. 2005).

HA dermal fillers as a group are very well tolerated. Infection can occur but is rare. Hypersensitivity reactions are also uncommon, and may result from reaction to the cross-linking agent used to stabilize the HA. Occasionally HA can be palpated, or a blue-gray tinge can be seen in the area of injection. This can be the result of superficial injection allowing more water binding in the dermis which selectively reflects blue wavelength of light making it appear darker than the surrounding skin. Solutions to this problem can be addressed by camouflage with makeup, needle puncture, and massage of excess gel from the dermis or injection of hyaluronidase. Injection technique can lead to clumping of HA especially in the lips. Massaging the area immediately following injection is the best way to prevent lumps from persisting. It is important to have patients understand the expected clinical course of swelling, firmness, and then softening which typically occurs over the course of 1 week. One of the benefits of using HA for the less experienced user is the fact that they can be readily broken down by the hyaluronidase (Newman 2009).

The most frequent types of reactions are needle marks at the site of injection, erythema, swelling, tenderness, mild pruritus, bruising, and small lumps/bumps. These are generally mild

and are usually transient. These reactions should be discussed in detail with the patient before treatment so that they are considered expected rather than true complications (Beasley, Weiss et al. 2009).

True complications are rarely seen when injecting HAs, but many of these complications directly correlate with the skill and experience of the physician-injector. These true complications include injection into or compression of vascular supply, tissue necrosis, persistent nodule formation, granuloma formation, allergic reaction, infection, and visible blue hue (Tyndall effect). It has been well documented that nitropaste and hyaluronidase must be readily available in the physician´s office for the immediate treatment of any vascular compromise. Hyaluronidase and extrusion techniques are also helpful for treating persistent nodules and the Tyndall effect (Beasley, Weiss et al. 2009).

The management of dermal filler complications is summarised in an article of C. Winslow. Bruising is a potential complication to all fillers. The potential to bruise can be affected by needle size, location of infection, and type of filler. Medication such as aspirin, ibuprofen, or other anticoagulants may make the patient more susceptible to bruises. Herbal supplements such as fish oil, glucosamine, or chondroitin can also adversely impact bruising. Swelling is the most common and ubiquitous complication experienced with fillers. HA fillers are sugar molecules that bind and hold water and should be expected to cause more swelling than do other classes of fillers. Post-treatment ice application and elevation of there head may help. Patient troubled by swelling may benefit from short prednisone taper or antihistamines. Formation of lumps under the skin can occur due to the consistency of the filler, reaction to the product, or poor technique. Small lumps resulting from HA injection can easily be treated with hyaluronidase. Improvement can be seen within hours. The ability to contour the injection site after injection is unique to HA class and is attractive to many patients. Erythema after injection is common, especially if massage is performed immediately after filler placement. Some amount of pain during and after injection is common and can be prevented with topical numbing and/or nerve blocks administered before injecting the filler. Skin necrosis is a well known complication that has a predilection for certain “danger zone”. The dorsal nasal artery may cause compromise of skin at the alar region. Collagen and hyaluronic acid are commonly injected in the lips. Filler injections in the perioral area can induce cold sore formation by reactivation of the latent virus. Stress, swelling, and massage may also contribute. Patients with a strong history of cold sore activation or those who had cold sores with prior injections should be treated with an antiviral such as acyclovir. Infection is fortunately quite rare after filler injection in an acutely inflamed area, such as skin with active acneic breakout. Focal or systemic infections should be considered a contraindication to injection. True allergic reactions are quite rare with HA. Immediate allergic reactions are manifested by significant swelling, itching, and pain. Swelling may involve the oral cavity, lips, and tongue, depending on the severity of reaction and location of injection. Skin testing for HA is not standard or required but should be considered in atopic individuals. Despite its rare nature, hypersensitivity to HA or its derivatives of its preparation may still be seen in < 1 % of patients injected. Granulomas typically appear late, months or years after injection, and remain localized to the injection site. They are typically soft and dark red or purple. Intralesional steroids remain the mainstay of granuloma treatment. The most dreaded complication because of its unsightly nature and permanence, a scar can result from injection or a complication thereof. Treatment of scares

includes intralesional steroid, pulsed dye laser or pulsed light treatments, pressure, and silicone (Winslow 2009).

Whilst it is true that HA is tolerated extremely well, it is not uncommon (12 %) to observe transient erythema and mild swelling. Other documented complications include a case report of a clinical picture similar to a sterile abscess over injection sites and injections of any form may trigger sarcoidosis at the injection site, and HA has not escaped. A recent review also quoted an overall significant complication rate of 1 in 1600 applications. The mild tissue reaction seen with many injections may, on occasion, be so profound as to elicit a formal inflammatory response and a range of reactions has been documented, varying from simple hypersensitivity, to angioedema with positive titres of anti-HA immunoglobulin G and E (Price, Berry et al. 2007).

Depth of dermal filler placement is particularly important in preventing discoloration. Novice injectors occasionally inject too superficially causing a blue-gray discoloration known as the Tyndall effect. The Tyndall effect refers to the fact that different wavelengths of light scatter depending on the size of substances they encounter. According to Rayleigh scattering, for sufficiently small particles, the amount of light scattered is inversely proportional to the fourth power of wavelength. For example, blue light is scattered more than red light by a factor of (700/400) = ~ 10. Thus, within the skin, long red wavelengths penetrate deeper into the tissue while shorter blue wavelengths are more easily scattered and reflected outwards. The incidence of the Tyndall effect is most likely to occur if filler meant to be injected deeply is injected too superficially in the skin. The high-risk areas include the so-called I zone of the central face, (the nasojugal folds, nasal dorsum, and lip), the infraorbital troughs, and fine superficial lines such as periorbital and perioral rhytids ("crow's feet" and "pucker lines") (Hirsch and Stier 2008).

Studies reported injection-related reactions, including redness, swelling, darkening of the treatment site, and slight pain in about 13 percent of patients. Ongoing analysis of the adverse event databases indicated that in 1999, with an estimated 144,000 patients treated with Restylane, only one of every 650 (0.15 %) reported redness, swelling, localized granulomatous reactions, bacterial infection, or acneiform lesions. Delayed implant hypersensitivity reactions were reported in several case series at low incidences (0.4 to 3.7 %) in early (before mid-1999) non–United States use of Restylane. In mid-1999, a hyaluronic acid raw material with trace amounts of protein six times lower than the raw material previously used was introduced. The amount of protein in the more purified product was reported to be in the range of 13 to 17 g/ml of product. In contrast to 1999, reported adverse events were reduced to 0.06 % and hypersensitivity reactions were reduced to 0.02 % in 2000 (Matarasso, Carruthers et al. 2006).

6.3.2 Safety of Macrolane™

In the recent prospective, open-label, noncomparative, multicentre study of De Meyere et al, 61 patients were treated with Macrolane™ VRF30. The study participants could receive one touch-up treatment up to 8 weeks following the initial injection. The incidences of expected events (tenderness, pain, swelling, itching, redness, and bruising – occurrence within the firs two weeks after treatment) were 34.4% (bruising) to 80.3% (tenderness). An increased number of the subjects showed a tendency to report swelling, pain, and redness when a higher volume of

stabilized HA gel was injected. Most events (>80 %) were mild to moderate in intensity and resolved after a mean duration of 7 days. During the entire 24-month follow-up period, 39 % of the subjects did not report any adverse events, whereas 34 % of the subjects reported 37 treatment-related adverse events during the 24 months after treatment. None of the adverse events assessed by the investigator as related to treatment were serious. The most common treatment-related adverse event was implantsite swelling, which occurred for five of the subjects (mean time to onset=4.4 days; mean duration=76.8 days). Implant-site swelling was reported as an adverse event only if it lasted more than 2 weeks. Injection-site pain, implant-site pruritus, and implant-site haematoma occurred in four patients each (mean time to onset=3.5 to 5.5 days; mean duration=17.3 to 28.7 days). The 37 treatment-related adverse events included one infection of moderate severity, which resolved after treatment. The infected subject had received prophylactic antibiotics before treatment. None of the subjects who received no prophylactic antibiotics before treatment experienced posttreatment infections judged to be treatment related by the investigator. Investigator assessment of capsular contracture to determine consistency, tenderness, and appearance showed that 1 month after initial treatment and touch-up treatment, 50–60 % of the subjects had slightly firmer buttocks, with 18 % of the subjects still showing slightly firmer buttocks at 6 months. Capsular contracture rates were minimal up to 24 months after treatment, at which point, 98 % of subjects were graded as having normally soft buttocks. During the entire study period, only one subject had abnormal-looking firm buttocks 12 months after treatment. The subject felt no pain or discomfort from this, and the buttocks had returned to normal softness by the 18-month visit. Local displacement of the injected material into the injection tunnel was reported in two subjects but resolved spontaneously and required no action. A third subject with a low BMI (19 kg/m2) experienced dislocation of the gel outside the buttock, with formation of a small nodule cranially toward the iliac crest and also a nodule laterally toward the tensor fascia lata. After removal of the scar at the injection point, this dislocation was easily resolved by pressing out the gel through the incision hole and by the injecting 3,000 IU of hyaluronidase dissolved in 100 mL saline using a 15-cm infiltration cannula (De Meyere, Mir-Mir et al. 2014).

Incidences of safety-relevant records were similar in other clinical trials. Heden et al treated 56 patients with Macrolane™ VRF30. No serious adverse events were reported, and the majority of treatment-related adverse events (58/69) were mild to moderate in intensity and transient in nature. The most commonly reported treatment-related adverse events were anticipated postinjection reactions such as injection-site pain (17 events) and injection-site reactions (swelling, tenderness, and/or redness; 13 events). These events typically occurred after injection, were of mild to moderate intensity, and resolved within 3 weeks. Six instances of fever also occurred, beginning at most 1 day after treatment and lasting 2 to 6 days. Antibiotics were used to treat these cases (Heden, Sellman et al. 2009).

After injection of Macrolane™ VRF20 into the back of the hands in one patient, there were no signs of any side effect (Hartmann, Bachmann et al. 2010).

Macrolane™ is also intended for contouring of calves. One case report on an adverse reaction after calf contouring is available. Chaput et al reported on a severe cellulitis in a patient having received an injection of Macrolane™ in her calf. The authors strongly recommend the conduction of such injections in a surgical environment (Chaput, Eburdery et al. 2012).

6.3.3 Risk analysis

A comprehensive risk analysis for the products under discussion has been performed. Thereby, potential risks have been addressed and discussed. In the risk analysis, hazards and their clinical consequences have been characterised according to the putative harm for patients and probability of occurrence. Risk-diminishing measures have been taken. For more detailed information, reference is made to the risk management file, which is part of the technical documentation. From a technical, biological, and clinical point of view, the residual risk for clinical use of Hyacorp MLF1, Hyacorp MLF2, or GeneFill Contour is tolerable after implementation of risk-minimising measures. There are no inacceptable risks associated with Hyacorp MLF1, Hyacorp MLF2, or GeneFill Contour.

7. Post-market data

Product	**Certified since**	**Units sold in EU (until July 2014)**	**Units sold outside EU**	**Serious adverse events or incidents reported**
Hyacorp MLF1	2013	1880	3810	-
Hyacorp MLF2	2013	1321	6393	-
GeneFill Contour	2013	1206	1935	-

8. Conclusion

During the last few decades, the demand for techniques to enhance or alter body surfaces and contours has increased for both medical and aesthetic reasons.

Compared with surgical procedures, minimally invasive procedures offer several benefits with regard to avoidance of general anaesthesia and hospitalisation, reduction of risk of infection, alleviation of trauma, and recovery time. Injectable products are considered to have a good predictablility and facilitate corrective actions.

Fat transfer is widely accepted treatment option. In many ways, fat is an ideal filler, in particular since it is highly biocompatible. However, one limitation is the need for donor material which can be a problem when the patient do not wish to undergo or is unsuitable for liposuction.

Cross-linked hyaluronic acid products offer several distinct advantages over permanent filler. Because HA oocurrs naturally in the human body, its biocompatibility is excellent. Multiple clinical records confirm the high overall safety profile of BDDE-cross-linked HA fillers. One

great advantage is the possibility to reverse the effects either by hyaluronidase injection or by removing the HA from the implant site through aspiration. Furthermore, its administration is minimally-invasive and its performance is well-established for decades.

Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour are regarded to be equivalent to the currently used and well established products Macrolane™ VRF20 and Macrolane™ VRF30 from a technical, biological, and clinical point of view. Therefore the scientific literature discussing these products was analysed. Macrolane™ gained has been certified as medical device in the EU in 2006. Macrolane™ VRF20 and Macrolane™ VRF30 were investigated in several prospective studies and case studies. The trials were performed during 2009 and 2014. The performance of Macrolane™ can be assessed as appropriate leading to high satisfaction in patients and physicians. In summary, performance of Macrolane™ VRF20 and Macrolane™ VRF30 has been proven. According to MEDDEV 2.7/1 rev3 and based on the principle of equivalence, performance of Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour can be regarded as demonstrated.

Articles related to the safety of hyaluronic acid in general, and especially to the Macrolane™ products report only a very low rate of side effects and complications. No unexpected side effects, complication, or incidents related to these products were reported. Based on the data on Macrolane™ VRF20 and Macrolane™ VRF30provided there are no concerns related to the safety of these products.

Performance and safety of hyaluronic acid have been well supported by additional review articles issued during the last years.

The post market surveillance of Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour reflect their status of safety reported in scientific literature for the equivalent products Macrolane™ VRF20 and Macrolane™ VRF30. No harm to patients has been reported during the last years.

In summary hyaluronic acid as filling agent provides a suitable performance and a high safety in patients. Hyacorp MLF1, Hyacorp MLF2, and GeneFill Contour are equivalent to the well established products Macrolane™ VRF20 and Macrolane™ VRF30. Performance and safety can be demonstrated by these products. The benefit-to-risk ratio for clinical use of the products under discussion within their indications is considered to be positive.

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Product Management

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10. Attachments

Attachment 1 - Literature Search and Outcome
Attachment 2 – Equivalence Analysis