Health Canada Santé Canada

GUIDANCE DOCUMENT

Preparation of Premarket Medical Device Licence and Licence Amendment Applications for Dermal Fillers

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

TABLE OF CONTENTS

1.0 INTRODUCTION

This guidance document is intended to aid manufacturers and regulatory representatives in preparing medical device licence applications for dermal fillers.

All Class III and IV medical devices, including dermal fillers, require a review of submitted evidence of safety and effectiveness before a licence can be issued. This guidance document provides details regarding the scientific and clinical content to be submitted in support of licence applications for dermal fillers.

The content described in this guidance document is to be submitted for review in addition to the general data elements listed in paragraphs 32(1)(a)-(e) of the *Medical Devices Regulations* (Regulations).

1.1 Policy Objectives

To facilitate the submission to Health Canada of the scientific and clinical content for dermal filler licence applications filed pursuant to sections 32 and 34 of the *Medical Devices Regulations*.

1.2 Policy Statements

Dermal fillers that do not contain animal or human tissue or their derivatives are classified as Class III medical devices.

Dermal fillers that are manufactured from or incorporate animal or human tissue or their derivatives are classified as Class IV medical devices.

1.3 Scope and Application

This document discusses information relevant to dermal filler devices.

The data and information requirements outlined in Section 2.1, 2.2, 2.3 of this document are applicable to both Class III and Class IV dermal filler licence applications, whereas information in Section 2.4 is only applicable to Class IV dermal filler licence applications.

This guidance document should be read in conjunction with Health Canada's guidance document "*How to Complete a New Medical Device Licence Application*".

Autologuous wrinkle fillers and biological drugs (for example [e.g.] Botulinum toxin) are out of the scope of this document.

1.4 Background

A copy of the Regulations is available on The Department of Justice Canada website as http://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/index.html.

The guidance documents listed below provide general information relevant to medical device licence applications and are available on the Health Canada website at http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php.

- *Recognition and Use of Standards under the Medical Devices Regulations*
- *How to Complete the Application for a New Medical Device Licence*
- *Guidance for the Interpretation of Section 28 to 31: Licence Application Type*
- *Guidance Document: Guidance for the Labelling of Medical Devices, not including in vitro diagnostic devices - Appendices for the Labelling of Soft Contact Lenses, Decorative Contact Lenses, and Menstrual Tampons*
- *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications V.2*
- *Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s*)

1.5 Definitions

Comparator: for the purposes of this guidance document, a comparator means a dermal filler licensed in Canada used as a reference in preclinical or clinical studies.

Predicate device: for the purposes of this guidance document, a predicate device is a previous version of the subject device made by the same manufacturer that is licensed in Canada.

Subject device: for the purposes of this guidance document, subject device means the actual dermal filler for which the medical device application is submitted.

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 Information Applicable to Class III and IV Medical Device Licence Applications

2.1.1 Device Description

A general description of the dermal filler should be provided, including: its appearance and intended use; its detailed composition; a description of its components, parts and accessories; and the materials used in its manufacture and specification of their origin (e.g., animal, human, synthetic, bacterial).

The following information should also be included when applicable:

- Specifications of the products that constitute the composition of the device (e.g., molecular weight);
- Final concentration of each component in the end product;
- All additives and cross-linking agents, including percent and degree of cross-linking; and
- If the device contains particles, the particle size range and size distribution.

Information related to the syringe and needle or cannula should be provided, including the name of supplier, material composition, syringe volume, length and gauge of the needle or cannula. A photograph or drawing of the device with all functional components clearly labelled may also be provided. In addition, a description of device packaging materials and configuration, especially those of the sterile barrier should be included.

2.1.2 Licence Amendments

If the application is for an amendment to a licensed medical device under section 34 of the *Regulations*, a description of the modifications (e.g., changes in composition, material specifications, manufacturing process, or indications for use) as compared to the predicate is required. A comparison of the key specifications between the subject device and the predicate device should be provided in tabular format.

2.1.3 Design Philosophy

A section on design philosophy should be included giving information related to features of the device, as well as a design concept and mode of operation of the device. In situations where the manufacturer decides to submit a comparison to a previously licensed dermal filler of similar composition, as additional supportive evidence of safety and effectiveness of a new or amended device, a detailed list of similarities and differences between the devices should be provided (tabular format is preferred).

2.1.4 Marketing History

The marketing history of the subject device should be provided and include information on the total number of device units distributed worldwide, a list of countries or geographical regions where the device has been sold with details on numbers of units sold in each country or geographical region. A summary of reported problems and complaints with the device, as well as details of any recalls and actions taken to resolve the problems, is required. When applicable, information on the regulatory status of the device in other countries should also be provided in this section. When the device is

compared to a predicate device with similar composition and licensed by Health Canada, marketing history of this predicate should also be submitted.

2.2 Safety and Effectiveness Requirements

2.2.1 Material Specifications

When applicable, the following information should be provided:

- Certificates of analysis and/or materials safety data sheets (MSDS) and/or certificates of conformity to a recognized standard.
- The names of suppliers of materials that comprise the device.
- When cross-linking is used, the total amount of cross-linking agent in the finished product.

The manufacturing process should be validated and control procedures adopted to avoid variability in the final product quality. Acceptance criteria should be established to ensure that the product meets the specifications for material purity, homogeneity and consistency. To this end, the following information should be provided:

- The manufacturing steps, including a process tree illustrating the progression from starting materials to the finished product;
- Names of all reagents and processing steps used in the manufacturing process;
- The amount of any manufacturing impurities (e.g., organic solvents, heavy metals, cross-linking agents, protein and low molecular weight oligomer contaminants, and bacterial by-products) in the final device.

The names identifying each compound comprising the device should be used in a consistent manner throughout the document or equivalent names must be clearly defined.

2.2.2 List of Standards

A list of standards applied in whole or in part to the manufacture and design of the device should be included.

For more information, please refer to Health Canada guidance document, *Recognition and Use of Standards under the Medical Devices Regulations* at: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/md_gd_standards_im_ld_normes-eng.php.

The manufacturer should indicate whether or not the device complies with the policies, guidelines or voluntary standards of a recognized authority in terms of material, design or performance. The full title, version or identifying number, date and responsible agency of each standard must be provided in a tabular format.

2.2.3 Preclinical Studies

All studies, including chemical, physical, mechanical, biocompatibility, and animal studies should be performed on the **final sterilized product**.

2.2.3.1 Device Characterization

Data related to key chemical, physical and mechanical characteristics of the device should be provided. Acceptance criteria should be established for each significant parameter and a discussion should be included to justify the selection of parameters and the adequacy of the acceptance criteria.

2.2.3.1.1 Chemical Characterization

Chemical Residuals

Residues and impurities including cross-linking reagents, if applicable, should be identified and quantified after exhaustive extraction of the final sterilized device. Sample preparation may be conducted according to ISO 10993, "*Biological evaluation of medical devices - Part 12: Sample preparation and reference materials*".[1]

The manufacturer should ensure the selection and use of appropriate analysis methods to detect and quantify all releasable chemicals such as organic solvents, heavy metals, cross-linking reagents, low molecular weight oligomer contaminants, and bacterial by-products. Experimental methods should be described and detection limit sensitivities specified.

An estimate of the expected upper limit of patient exposure to chemical residuals, including cross-linking reagents, should be specified based on the worst case estimate of the number of repeated injections and volume of product injected. Based on the no-observed-adverse-effect level (NOAEL), the safety factors for toxicity for potential toxic chemical species should be presented and discussed.

Device with a Drug Substance

If the device contains a drug component, evidence that the drug meets the specifications of pharmacopeia stated in schedule B[1] of the Food and Drugs Act and GMP certificate should be provided.

Evidence showing that the drug remains stable and active in the finished product should also be included.

2.3.1.1.2 Physical and Mechanical Characterization

Key physical properties relevant to the device should be assessed by conducting appropriate testing. Examples of testing include:

Degree of Material Modification

The degree of material physical or chemical modification can have a significant effect on the properties of a filler material. When applicable, information should be provided on the type of modification performed on the material and the degree of modification specified (e.g., cross-linking and degree of cross-linking).

Device Rheological Properties

Viscosity can be determined as a function of shear rate to represent conditions such as when the material is injected into the dermis or injected through a small bore needle.

Extrusion Force Testing

This test should be performed to study the ease of injectability of the product through the smallest needle to be used with the device.

[1] As per Schedule B to the *Food and Drugs Act* :
European Pharmacopoeia (PH.Eur.)
Pharmacopée française (Ph.F.)
Pharmacopoeia Internationalis (Ph.I.)
The British Pharmacopoeia (B.P.)
The Canadian Formulary (C.F.)
The National Formulary (N.F.)
The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
The United States Pharmacopoeia

Characterization of Particulate Phase Fillers

When a device contains particulate matter, whether resulting from cross-linking of the same material or from suspending particles in a fluid or gel phase, the average size and size distribution of particles, concentration of particles in the product, and homogeneity of the particles distribution within the device should be determined.

2.2.3.2 Biocompatibility Tests

Biocompatibility tests are required to determine whether the device materials are associated with any local or systemic adverse effects.

Biocompatibility tests should be selected based on the ISO 10993-1, "*Biological evaluation of medical devices - Part 1: Evaluation and testing*". This document encompasses a series of standards for biological evaluation of medical devices for a number of characteristics including cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, mutagenicity or genotoxicity, hemocompatibility, subchronic toxicity and chronic toxicity.

A summary of biocompatibility tests should be provided for Class III dermal filler devices, including: the tests conducted, the standards applied, the test methodology, the pass/fail criteria chosen with justification, and a summary of the results and conclusions drawn. For Class IV devices, a full biocompatibility study report is required, accompanied by a comprehensive summary that includes all the information listed for Class III submissions.

2.2.3.3 Pyrogenicity Testing

Pyrogenicity testing in accordance with ISO 10993-11, "*Biological evaluation of medical devices - Part 11: Tests for systemic toxicity*" should be considered in the evaluation of dermal fillers. A justification for the selection of the testing method should be provided, and it should cover both material-mediated and endotoxin-mediated pyrogenicity. Results and conclusions as to device compliance with the acceptance criteria should be presented. Where pyrogenicity testing is not performed, adequate justification should be provided.

2.2.3.4 Animal Studies

Animal studies may be used when other available information is not sufficient to support some specific claims, such as device longevity, degradation and resorption or absorption. Animal models may also be used to study tissue reactions to the device.

A detailed description of the protocol should be provided for each animal study. The animal model, injection site and study duration should be representative of the conditions of use for the subject device. Histopathological evaluation reports should be included. After injection of the dermal filler, attention should be paid to the assessment of inflammatory response over time. The nature of tissue and cellular reactions, including the occurrence of device encapsulation, should be defined and cell types should be characterized and quantified for each study period. Device resorption or stability and device migration may also require assessment, as applicable, depending on the nature of the device, indications for use claims, location where the product is injected, etc.

2.2.4 Clinical Studies

Clinical data obtained from use of the subject filler on investigational test subjects are required in order to address safety and effectiveness questions that are not resolved through preclinical studies. Adequate clinical data should be provided to support each of the specific indications for use and claims of the device, and to identify any adverse events that may occur during clinical application of the device.

2.2.4.1 Study Design and Statistical Issues

A full copy of the study protocol should be provided. This includes explanations of the study objectives, descriptions of primary and ancillary hypotheses, definitions of the study population (that is [i.e.], inclusion and exclusion criteria), methods of randomization and blinding (if used), number and location of investigational sites, and enrollment procedures. Pass/fail criteria should be defined and a rationale supporting clinically meaningful endpoint(s) improvement included (e.g., extent of clinical improvement and significance as compared to baseline). Study endpoints should be clearly stated and should include both safety and effectiveness parameters. Clinical reports should include adequate justification for the bench marks used for assessing the effectiveness and for the safety endpoints.

Statistical methods for the analysis of data generated during the study should be described. Sponsors are encouraged to consult a statistician in order to identify the most appropriate study design and analysis method.

All indications and contraindications for use of the device should be consistent with the inclusion and exclusion criteria of the study. Total follow-up period, number of follow-up visits and interval between visits should be reported. Site of injection and quantity of product injected into each location should be specified for each patient. When patients receive additional injections during the study, the following should be specified: number

of patients who have received re-injections, number of re-injections each patient has received; injection sites; quantity of product injected; and when the re-injections occurred.

The number of patients enrolled in the study should be based on a statistical power analysis to ensure that the sample size is adequate to meet the study objectives. The statistical justification for sample size should take into account expected patient drop-out rates and the ability to detect specific adverse events. Losses to follow-up or drop-out should not exceed 10%. Patient follow-up duration should be determined based on the expected duration of product treatment effect, onset of typical adverse events, and existing knowledge of the safety profile of the material *in vivo*.

To avoid patient selection bias and other confounding factors, randomized, controlled multicenter study design is highly recommended. For the control group, a justification for the choice of device is required. A comparison of both safety and effectiveness data between the treatment and control groups should be provided. A dermal filler licensed in Canada, with similar indications for use, may be used as a valid comparator. In such a case, the data should demonstrate that the subject device is at least as safe and effective as the marketed device. Alternately, a single arm study may be pursued, provided that a thorough justification is included demonstrating its adequacy in supporting safety and effectiveness of the device and should include comparison to well established historical controls.

2.2.4.2 Safety Assessment

Patients should be monitored and evaluated regularly for occurrence of any complications and adverse events. Patients may also be provided with diaries to record events that might occur between follow-up visits.

The following should be assessed and reported for each follow-up visit:

- All complications and adverse events, including the total number and rate of occurrence of complications or adverse events, as well as the number and rate of specific complications or adverse events;
- Incident numbers or rate of occurrence should be provided for each treated facial location, when applicable;
- Adverse events should be categorized according to reported severity and relevancy to the device or the procedure along with the justifications for the conclusion;
- Information related to post-injection time to event occurrence, event duration, resolution status (whether ongoing or resolved) and action taken to address the problems; and

- Incidence of complications, nature and rates of events should be compared to a control group of patients or a control device, if applicable.

2.2.4.3 Effectiveness Assessment

An effectiveness assessment should be conducted at each follow-up visit and the following should be reported:

- Satisfaction scoring for patients and investigators;
- Improvement from baseline;
- Significance of improvement results;
- Duration of effect compared to manufacturer's claim, if applicable;
- Patients who received touch-ups or any other treatment (e.g. to resolve an adverse event) should be identified.

Note: When photographs of the patient's face before and after treatment are used, they should be assessed by a credible third party in order to avoid bias.

2.2.4.4 Data Analysis

Study data should clearly demonstrate whether the study endpoints were met or not. Detailed information should be presented for patients lost from follow-up, including reasons for the drop-out and the safety and effectiveness outcomes of the patient at the last follow-up.

2.2.5 Process Validation Studies

Process validation studies are required to validate the performance, adequacy, reproducibility and effectiveness of relevant procedures to be used in the manufacturing process, as it applies to the device.

Both Class III and Class IV devices require validation of sterilization, packaging and shelf-life; other validation studies may be required depending on the type of device.

2.2.5.1 Sterilization

Information related to the sterilization process validation should be provided, including but not limited to, the method of sterilization and specification of cycle parameters; the detailed sterilization protocol and specification of the standard method applied to process validation; the testing results; and the Sterility Assurance Level (SAL). The study should demonstrate that the sterilization method will achieve a SAL of at least 10^{-6}.

Important note: The manufacturer should ensure that the sterilization process does not alter the integrity and expected performance of the device. Device characterization should be performed on a finished sterilized device as supportive evidence that the sterilization process does not affect the properties of the device and compliance to specified acceptance criteria.

2.2.5.1.1 Radiation Sterilization

If radiation sterilization is used, the minimum and maximum sterilization doses should be specified. The manufacturer may use applicable Standards, such as ANSI/AAMI/ISO 11137-1, "*Sterilization of health care products. Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*", and ANSI/AAMI/ISO 11137-2, "*Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose*".

2.2.5.1.2 Ethylene Oxide (EtO) Sterilization

When sterilization with ethylene oxide is used, residual levels of ethylene oxide (EtO), ethylene glycol (EG), and ethylene chlorohydrin (ECH) remaining in the device after the process should be determined, and evidence should be provided that the levels of residuals are acceptable. This determination may be based on ISO 10993-7, "*Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals*".

The EtO sterilization validation may be based on adequate Standards such as AAMI/ISO 11135-1, "*Sterilization of health care products - Ethylene oxide - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*".

2.2.5.2 Packaging Validation

A packaging validation report should be submitted as part of the medical device licence application. All packaging components should be described, including the syringe and materials used to protect the device. Packaging should be validated, in conformity with established acceptance criteria, with respect to maintaining device properties and sterility for the duration of the proposed shelf-life. Evidence to support packaging stability during normal transport, storage and handling should also be presented.

2.2.5.3 Shelf Life Validation

The shelf-life of the product should be clearly stated. Data supporting the expiration date for the product should be submitted. Such data should be collected from at least three product lots. Stability validation studies should assess the critical specifications of the

device to ensure that the device meets all of the original acceptance criteria for the duration of its shelf-life, under predefined device storage conditions.

It is recommended that the manufacturer provide testing data from real-time aging of the device. Alternatively, the accelerated aging method can be used, in which case an appropriate justification should be included to demonstrate that the data from accelerated aging conditions are representative of the real-time aging conditions, based on device materials, packaging, sterilization method, and storage conditions.

2.2.6 Literature Studies and Bibliography

A summary of published literature relating to the use, safety and effectiveness of either the subject device or a marketed device with similar composition and identical indications for use should be provided. When published studies are used to support the safety and effectiveness of the subject device, a copy of the articles should be included. In addition, a side by side comparison of the subject and the referenced device should be provided.

A list of references of the studies should also be included.

2.3 Labelling Requirements

Copies of the device labelling (as well as advertising and marketing materials, if available) should be provided, including device package insert or Instructions for Use, package labels technical brochures, and instructions to patients and physicians.

Device package labels should include the device name, identifier, material, volume, expiration date, sterilization status and method, and the manufacturer's name and address.

The Instructions for Use should include the following: device name, a brief device description with material information and content, indications for use, a list of contraindications, warnings, precautions, and possible adverse events.

2.3.1 Indications for use

The indications and intended use should be stated consistently throughout the labelling and marketing material in the application. The statement of indications for use should specify target populations or clinical conditions, when applicable. The specific site of injection (e.g. lips, nasolabial folds, marionettes), as well as depth of injection (e.g. mid dermis, deep dermis, superficial subcutis injections) should be identified. The expected duration of the treatment effect may also be stated.

2.3.2 Contraindications

The contraindications should identify any patient population, patient conditions or anatomical sites where the dermal filler should not be used, including the following that may be addressed in this subsection:

- Lactating and pregnant women;
- Children;
- Patients with hypersensitivity to any of the device materials;
- Patients with bleeding disorders;
- Injection in the breasts and nipples;
- Incompatible medical and psychological conditions of the patient, including unrealistic expectations;
- Patients susceptible to keloid formation, hyperpigmentation or hypertrophic scarring;
- Tissue with infection or inflammation;
- If the dermal filler contains drugs, a statement that the dermal filler is contraindicated in patients with known hypersensitivity to the drugs being used. Also, the device should be contraindicated in patients taking medication that may interfere with the anaesthetic.

2.3.3 Warnings and Precautions

The following warnings and precautions are applicable to all dermal fillers, and should be listed in the Instructions for Use:

- The risks of potential complications associated with intravascular injection;
- Avoid injection into blood vessels;
- Injection into patients with a history of previous herpetic eruption may cause reactivation of the herpes;
- Injection of the device where there is a possibility of interaction with a previously injected dermal filler;
- A statement that the device should only be injected by a qualified medical practitioner who has sufficient training with the use of the device; and
- A statement that the patient should be given sufficient information regarding the potential adverse events and complications related to the device to be able to make an informed decision concerning treatment.

Additional warnings and precautions may be applicable to specific devices and may also be addressed in this subsection.

2.3.4 List of Adverse Events, Limitations and Complications

General and device-specific limitations and complications, as well as known and potential adverse events, should be listed in the labelling. Typical adverse events and complications may include, but are not limited to: pain, swelling, itching, bruising, numbness, lumps and bumps, nodule formation, granuloma formation, allergic reactions, infection, and migration.

2.4 Additional Requirements for Class IV Dermal Fillers

Dermal fillers manufactured from or incorporating animal or human tissue or their derivatives are classified as Class IV devices. Licence applications for these devices should not only include the information outlined in sections 2.1, 2.2, and 2.3 of this guidance document, but also meet the information requirements for Class IV medical device applications as outlined in the guidance document *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications*. The following highlights the typical additional information requirements for Class IV dermal filler submissions, for more complete guidance on these elements, refer to the above mentioned guidance document:

- **Section 32(4)(d):** A risk assessment comprising an analysis and evaluation of risks, and the risk reduction measures adopted to satisfy the safety and effectiveness requirements.
- **Section 32(4)(e):** Device quality plan should be provided to specify quality practices, resources and sequence of activities relevant to the device. This information may be provided in the form of a flow chart, process map, document matrix, table or text description. The quality plan as described in ISO 10005 provides a mechanism to tie specific requirements of the product, project or contract to existing generic quality system procedures. It is not intended to duplicate the device-specific information requested under section 32(4)(f).
- **Section 32(4)(g):** The manufacturing process of the device.
- **Section 32(4)(j):** Detailed biological safety information for devices manufactured from or incorporating animal or human tissue or their derivative, substantiating the adequacy of the measures taken with regard to the risks associated with transmissible agents.[2] This is to include viral clearance results for known hazards. Donor screening concerns must be fully addressed. Methods of harvesting and long-term registries must also be fully described. Process validation results are required to substantiate that manufacturing procedures to minimize biological safety risks are in place.

References

1. ISO 10993, "*Biological evaluation of medical devices - Part 12: Sample preparation and reference materials*".

2. *Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s).* http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/anim_tiss-eng.php