Health Canada Santé Canada

MASTER FILE PROCEDURES

Natural Health Products Directorate

August 2006
Version 1.0

Canada

“Our mission is to help the people of Canada maintain and improve their health, while respecting individual choices and circumstances.”

Health Canada

“Our role is to ensure that Canadians have ready access to natural health products that are safe, effective and of high quality while respecting freedom of choice and philosophical and cultural diversity.”

Natural Health Products Directorate

Également offert en français sous le titre :
Fichier principal : procédures, particularités et spécifications

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1. INTRODUCTION

A Natural Health Product Master File (NHP-MF) is a reference document that provides proprietary information about the relevant manufacturing details and/or the technical specifications of the medicinal ingredients/raw materials that are used in the manufacturing of a natural health product (NHP) meant for human consumption. This may include specific processes involved in the manufacturing, processing, and packaging of raw material/medicinal ingredients (or other materials which are proprietary in nature) used in a NHP for human use.

The NHP-MF is a mechanism that would enable a manufacturer of a medicinal ingredient/ raw material to provide proprietary information on their product directly to the Natural Health Products Directorate (NHPD) without disclosing the information to the applicant. The NHP-MF mechanism is applicable to medicinal ingredients, non-medicinal ingredients, (packaging material and safety and efficacy evidence data) in support of Product Licence Applications or Clinical Trial Applications. Cross-reference can be made to NHP-MFs by one or more manufacturers (as long as an authorization letter from the Master File originator (holder) is provided to NHPD in advance or provided along with the product licence application).

(Note: Information in the Master File should only be either proprietary in nature, or information which will be cross-referenced by other applicants to be assessed at one time to avoid repeated assessment).

This guidance document provides:

- a description of administrative procedures related to the NHP-MFs;
- the requirements for the submission, amendment, cancellation, update and transfer or change in the holder of a NHP-MF;
- a description of the procedures used by the NHPD to process NHP-MFs; and
- a list of the information that should be submitted.

2. ADMINISTRATIVE PROCEDURES RELATED TO NHP-MFS

All NHP-MFs are kept in strict confidence by Health Canada and only officials who have proper authorization will have access to the master file. Health Canada does not reveal the status or content of the Master File to non-authorized individuals or companies.

The NHP-MF should be sent in either English or French to the following address:

2.1 Forwarding Address

Chief, Submission Management Division
Bureau of Product Review and Assessment
Natural Health Product Directorate
Qualicum Tower A
2936 Baseline Rd
Ottawa, ON K1A OK9
AL 3302B

Courriers: K2H 1B3
Fax: (613) 954-2877

2.2 Name and Address

The NHP-MF must include the following information:

- name and address of authorized agent/appointed representative (Product Licence Applicant);
- name and address of corporate headquarters; and
- name and address of manufacturing, processing, and packaging facilities.

2.3 Official Language of Correspondence

The NHP-MF may be submitted in English or French.

2.4 Confidentiality

The NHP-MF is a confidential document; only authorized officials of Health Canada (NHPD) have the permission to access the file.

3. REVIEW OF NHP-MFS

3.1 Medicinal Ingredients and/or Non-medicinal Ingredients

All proprietary information is reviewed as part of the NHP-MF. All non-proprietary information is reviewed as part of product licence application and is considered to be non-confidential. Comments concerning deficiencies in the proprietary information contained in a NHP-MF are sent directly, in writing, to the manufacturer or its appointed representative/agent. Comments concerning deficiencies in the non-proprietary information part of the submission are sent to the applicant.

3.2 Names

Indicate the proper names, chemical names and the manufacturer's research or code numbers for the NHP.

3.3 Manufacturer

Indicate the name and address of the manufacturer that actually manufactures the medicinal or non-medicinal ingredient. If more than one company is involved in the synthesis or manufacturing process of a NHP, describe the responsibilities of each company and what manufacturing processes are performed and under what name and address.

3.4 Method of Manufacture

3.4.1 Brief Outline

The information provided about a NHP prepared through a chemical process or synthesis should include a flow chart and a narrative description detailing the reaction sequence and showing all intermediates, quantities, conditions of reaction e.g. temperature, pressure, pH and any impurities. The information provided about a NHP produced by fermentation should describe the fermentation process in general terms which should include all the conditions as described earlier.

3.4.2 Detailed Description

Provide complete and detailed information on the method of manufacture of the NHP substance, including:

- a flow chart of the synthetic route or manufacturing process;
- a list of reactants, solvents, and reaction conditions;
- the specifications for all the materials used in the process and/or name of the references (e.g. compendial); and
- the quality control checks (or in-process controls) performed at each stage.

The steps taken and a detailed description of final steps for the methods used for isolation and purification of the NHP should also be included.

A full list of materials used in the manufacture of the NHP should be provided. This list should include all the ingredients, (catalysts, solvents, name and ingredients of the culture for fermentation, etc) used in the synthesis, fermentation, extraction, isolation, and purification steps, regardless of whether they undergo any change or are eliminated or removed during the process. If a proprietary substance (previously prepared ingredient or starting material) has been used as a component, the complete quantitative composition should be included.

Specifications for all the materials (medicinal ingredient, non-medicinal ingredient, and solvents) used in the method of manufacture of the NHP, including identity, purity, and potency, where applicable, should be provided. Special consideration should be given to potential isomeric impurities in the starting material, and the contaminants that could be carried through the synthesis to the final product.

The information provided about a NHP prepared by a chemical process or synthesis should include:

- a detailed description of each chemical reaction (synthetic step), describing typical reaction conditions used (time, temperature, catalyst, pressure, pH) **and/or** a flow chart of the reaction sequence, showing all intermediates, which should include all the reaction conditions;
- names and amounts of all substances used in the process; and
- percent yield for each reaction in the sequence (if isolated not for *in-situ*.)

For synthetic duplicates, specifications for intermediates should be supplied, where the intermediates are isolated and controlled with respect to purity before proceeding to the next step.

The information provided about a NHP produced by fermentation should describe in detail the fermentation process, including:

- isolation of the constituent;
- source and type of micro-organism used;
- all the solvents used;
- precursors;
- time and temperature; and
- name and composition of preservatives.

A detailed description of the isolation and purification of the NHP is also required. If the product is sterile when prepared, a complete description of the method used to sterilize each batch and the sterilization conditions (e.g. temperature, pressure, humidity, time) and of the Good Manufacturing Practices controls used to maintain the products' sterility during storage and transportation should be provided. (The specifications developed should be used to make comparisons between the materials produced during pilot plant studies, which are often used in early trials, and the material obtained from full-scale production).

3.5 Structure Elucidation and Confirmation

Where appropriate, evidence is required for the confirmation of structure with such methods such as elemental analysis, ultraviolet, infrared, nuclear magnetic resonance, and mass spectroscopy (or any other appropriate test to confirm the structure of the compound.)

3.5.1 Physicochemical Properties

Provide the chemical structure, molecular formula, molecular weight, melting point, solubilities in the common solvents, and physical form (crystalline solid, liquid) of the NHP. Where appropriate, information should be supplied on polymorphs, pKa values, pH of aqueous solutions, solvate formation, particle size distribution and tautomers.

Note: Provide the relevant information appropriate to the product in the master file applicable to the product.

3.5.2 Impurities

A full description of the methods used to characterize and quantitatively determine the impurities including degradation products that are likely to be present as a result of the method of manufacture of the medicinal ingredient (raw material) or finished dosage form should be provided.

Information is required in the following areas:

- the impurities (manufacturing of the raw material i.e. isolate or chemically synthesized material), including degradation products (manufacturing of the dosage form), likely to be present from the method of manufacture;
- the impurities actually present; and
- the methods used to determine the quantities of impurities.

The impurities that are likely to be present from the method of manufacture - including reagents or solvents, starting materials or intermediates, and by-products from various steps - should be discussed in detail. A list showing structures of the possible impurities should be provided. Particular attention should be given to solvents (which are class 1 and class 2 solvents in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) residual solvent guidelines) such as methylene chloride, benzene, chloroform, pyridine, dioxin, anilines, and ethylene oxide and its products.

Predominant impurities (present at higher levels than the other impurities) or toxic impurities for which very low limits are required must be determined separately using impurity reference standards.

A description of the methods (high-pressure liquid chromatography, gas chromatography or other techniques) developed to assess the impurities should be provided. In some instances,

individual impurities may be detected by other techniques such as spectrophotometric methods. During the developmental work it is advisable to use more than one method for the detection of impurities so that the results obtained can be substantiated.

3.5.3 Reference Standard

If a reference standard has been used to identify, compare or quantify the medicinal ingredient, and if the method of manufacture of the reference standard is different from that described for the NHP, or if any additional steps are used for the purification, then it should be provided in detail.

Note: Reference standards are ultra pure materials developed by using the same synthetic scheme or any other synthetic scheme to obtain the same active substance which will be used for comparison purposes.

3.5.4 Specifications and Test Methods

Provide a copy of the proposed specifications, including the tolerance limits and the names of all test methods used. If the test methods used are specific and suitable for specific products, then the details of the test methods should be provided. No validation data is required but the test methods should be checked for specificity and reproducibility. The specifications should include physical characteristics in addition to tests for identity, purity, quantity or potency. A test or a combination of tests intended to limit the presence of impurities related or unrelated to the substance should be provided.

3.6 Safety and Efficacy

The applicant must submit any evidence to the NHPD that is not published, i.e. proprietary information not available to the public. The NHPD will maintain the confidentiality of this information.

Examples of proprietary information:

- results (both safety and efficacy) from in-house or sponsored etc. studies that have not been or may never be published (i.e. not been made available to the public);
- expert opinion reports;
- information on adverse reactions (i.e. number of case reports); and
- information from previous marketing experience (e.g. sales volume).