Health Canada Santé Canada

November 3, 2004

NOTICE

Our file number: 04-121869-138

Health Products and Food Branch Proposals for Summary Basis of Decision (SBD) and Notice of Decision (ND) Documents: Devices

The Health Products and Food Branch (HPFB) is, by this notice, clarifying its intent with respect to the development and publication of Summary Basis of Decision (SBD) documents, following the issuance of a corresponding Notice of Compliance (NOC) or Medical Device Licence. The SBDs will outline the scientific and regulatory-based reasons for Health Canada's decisions to grant market authorization for a drug or medical device.

In a Notice posted March 23, 2004, HPFB outlined its intent to electronically publish SBDs in a phased approach, beginning with New Drug Submissions (NDS) for New Active Substances (NAS) and a subset of Class IV Medical Devices. Health Canada can now confirm that this subset of Class IV devices will be comprised of New Class IV devices that relate to any one of the following: priority review applications, in-vitro diagnostic devices for donor screening, cardiovascular devices with novel technology (endovascular stenting systems, carotid stenting system and left ventricular assist devices) and new indications for use for cardiovascular and neurological devices. Preparation and publication of SBDs will apply to all device licence applications that are captured under the above scope and are licensed subsequent to January 1, 2005. It is the intent of Health Canada to publish SBD documents within four months of authorization for sale of a medical device.

Stakeholder consultations held June 10-11, 2004 in Ottawa solicited feedback on all aspects of the initiative, including the content of the documents and the strategy for phasing in submission types. Templates have been revised to reflect the feedback received from stakeholders; the medical device template is provided below for further comment. For information on the drugs SBD template refer to the HPFB Notice entitled *"Health Products and Food Branch Proposals for Summary Basis of Decision (SBD) and Notice of Decision (ND) Documents: Drugs"*. Interested parties should refer also to the Consultations Proceedings Report and Pilot SBD Exercise for Immulite 2000, posted to the Health Canada website September 28 and October 29, 2004, respectively.

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Notice of Decision

Further to feedback received from the June consultations, HPFB wishes to announce its intent to extend the Summary Basis of Decision initiative to include a proposal to publish Notice of Decisions (ND) at the time of Medical Device licence issuance. NDs are proposed to be published for the same scope of applications as those captured for SBD inclusion e.g. identified subset of Class IV devices for Phase One. The proposed ND would take the form of a one-page summary outlining the authorization received and general information related to the product. For additional information, please refer to Section 2 of the template below. The ND is proposed to be reproduced independently for publication at the time of license issuance as well as for inclusion in the overall SBD document.

Consultations with Sponsors

HPFB is proposing that prior to publication of each SBD, the sponsor have a two-week comment period to focus solely on the accuracy of the data and identification of any proprietary material included therein. Health Canada will make every attempt to ensure that commercially confidential information is not included. The templates provide sponsors with an indication of the material proposed for disclosure in each SBD and ND.

Any comments regarding the above information should be directed to Tara Bower, Policy Bureau, Therapeutic Products Directorate, within thirty (30) days, at the coordinates below.

By Mail
1600 Scott Street,
Holland Cross, Tower 'B',
2nd Floor, Address Locator 3102C5,
Ottawa, Ontario, K1A 1B6,

By fax to 613-941-6458

By email to tara_bower@hc-sc.gc.ca

Health Canada Santé Canada

SUMMARY BASIS OF DECISION (SBD)

MEDICAL DEVICE NAME

Manufacturer

Application No.

Licence No.

Date Issued	2004/10/26

Health Products and Food Branch

Canada

Our mission is to help the people of Canada
maintain and improve their health.
Health Canada

HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:

- Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch

Également disponible en français sous le titre: SOMMAIRE DES MOTIFS DE LA DÉCISION (SMD) NOM DE L'INSTRUMENT MÉDICAL Fabricant N° de la demande N° de l'homologation

FOREWORD

Health Canada's Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within reviewer reports. As such, SBDs are intended to complement and not duplicate information provided within the Operator's Manual.

Readers are encouraged to consult the Reader's Guide to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug and medical device submission/application review process is provided describing the factors considered by Health Canada during the review and authorization process of a drug submission and device licence application.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. For up-to-date information on a particular product, readers should refer to the most recent SBD or Operator's Manual for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Marketed Health Products Directorate (MHPD) website directly:
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/about-mhpd_e.html.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions. The information received in support of a Canadian device licence application may not be identical to that received by other jurisdictions.

Other Policies and Guidance:

Medical Devices - General:
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_devices_information_e.html

Management of Applications for Medical Device Licences and Investigational Testing Authorizations:
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/mdlappl-pol_final_e.html

General Enquiries (e-mail):
policybureauenquiries@hc-sc.gc.ca.

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1 DEVICE AND APPLICATION INFORMATION

Device name	
Manufacturer	
Medical Device Group	e.g., anesthesiology, cardiovascular, dental, gastroenterology & urology, general & plastic surgery, in vitro diagnostic, etc.
Biological Material	e.g., bovine pericardium, human serum, polyclonal/monoclonal antibodies
Combination Product	Yes [ ] No [ ]
Drug Material	e.g., heparin
Application Type and No.	e.g., new, amendment, priority
Date License Issued	
Device Catalogue/Model No.	If too long then refer to http://www.mdall.ca/
License No.	
Intended Use	E.g., authorized indication, target population, contraindications, limitation, etc.

2 NOTICE OF DECISION

The Notice of Decision should adopt the following paragraph structure:
The date of authorization, device description and principles of its operation, very brief description of supporting pre-clinical and clinical studies upon which authorization was based, the indication as it appears in the approved Package Insert, contraindications, and a final paragraph as follows: "Detailed conditions for the use of <device name> are described in the Package Insert. Based on the review of data on quality, safety and effectiveness, it is considered that the benefit/risk profile of <device name> is acceptable."

For licence amendment, complete the appropriate subsections affected by the change(s) only, and the corresponding Summary and Conclusion section(s). Indicate if the recommendation is that the licence be issued with terms and/or conditions.

If the device was reviewed under the Priority Review Policy, include a brief overview of the rationale for applicability of the policy.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Introduction

An introduction to the application, including a brief description of the disease/condition for which the device is intended for.

Brief description of the disease or medical condition for which the device is used. Marketing history, problem reports, racalls.

3.2 Device-Specific Detailed Information

Include information on:

- principles of operation
- description of the device
- components of the device
- materials used in the device and packaging
- reagent characterization: Characterization of the antibody(ies), antigens(s) used in the assay, if any recombinant/monoclonal technology was used in the preparation of the antibody (ies) or antigen(s), etc.
- if the device contains monoclonal or polyclonal antibodies, information on its source

- if the device contains a medicinal substance or drug, a description of the substance and its technical requirements
- include Health Canada's assessment of each section.

3.3 Devices Containing Biological Material

If the device is manufactured from or incorporates animal or human tissue or their derivative, include a general statement.

Example: "The <device name> consists of a single piece of bovine pericardium, sourced from <country name>. Health Canada has assessed the measures taken to mitigate risks associated with animal tissue being used in this device. A sterility assurance level (SAL) of 10^{-6} has been validated. A viral validation study conducted according to EC CPMP Note for Guidance on Virus Validation Studies (Feb. 1996) has shown an acceptable log reduction achieved by the manufacturing process. A risk assessment has been provided which shows acceptable risk mitigation for the risk of infectivity and hazards associated with the local host response to the presence of animal/human material including pyrogenic, immunological or toxicological responses."

3.4 Safety and Effectiveness

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment.

3.4.1 List of Standards

Provide a list of standards with full name and indicate the Health Canada's recognized standards for which a declaration of conformity was provided.

3.4.2 Method of Sterilization

- type of sterilization process used
- level of sterility
- A statement that an assurance and an attestation were provided stating that the process has been properly validated.

Example: "The proposed product is terminally sterilized in a steam autoclave at 121ºC for 35 minutes. The sterilization procedure meets the ISO 11134-1994 standard for terminal steam sterilization, and, the sterility testing demonstrates a sterility assurance level of at least 10^{-6}, and that the product remains sterile over the product shelf life."

Example: "The <device name> is sterilized using a 100% ethylene oxide (EtO) cycle, according to the ISO/AAMI/ANSI Ethylene Oxide Sterilization Standard 11135:1994 that has been validated to produce a sterility assurance level of at least 10^{-6}. Residuals are within acceptable limits."

3.4.3 Manufacturing and Quality Control

Manufacturing Process

Methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and, where appropriate, the installation of the device.

Example: "Material specifications, acceptance criteria and vendor certificates for the components of the <device name> were reviewed and found satisfactory.

The manufacturing processes for the implantable pacing lead, the steroid collar, and Parylene C coating were reviewed and found acceptable."

Process Validation Studies

List of processes for which information on validation was provided.

Example: "Information regarding process validation has been provided which included process system validation protocols for cleaning equipment, the capping process, the bead coating process, vial filling, capping and sealing and bar code label imprinting. Information has been reviewed and found satisfactory."

Quality Plan

Include a general statement such as "The quality plan was reviewed and found acceptable."

Quality System Certificate

Include a general statement such as "A quality system certificate (ISO 13485) issued by a Canadian Medical Devices Conformity Assessment System (CMDCAS) Recognized Registrars was provided."

3.4.4 Preclinical Studies

Physical Tests

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment. For example, physical testing conducted to predict the adequacy of device response to physiological stresses, undesirable conditions and forces, long-term use and known and possible failure modes, etc.

Example: "The *in vitro* bench testings included chemical analysis (ASTM Standard F90), balloon fatigue testing (standard ?), balloon distensibility test (standard ?), tensile strength and elongation test (standard ?), catheter preparation testing (standard ?), corrosion resistance testing (ISO 10555-1). All test results demonstrated that the <device name> has met the physical and mechanical design goals and are safe and acceptable for clinical use."

Biocompatibility Tests

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment. For example, studies conducted to ensure the device does not produce a toxic or immunological response in living tissue, such as irritation, sensitization, single dose, repeated dose, reproductive and development toxicity, pharmacodynamic and pharmacokinetic studies (if relevant), mutagenicity and carcinogenicity studies conducted, any other toxicological studies conducted, including those related to leachables, impurities, or metabolites.

Example: "All testing was conducted according to International Standard ISO- 10993, Biological Evaluation of Medical Devices Part - 1: Evaluation and Testing, for externally communicating devices that contact circulating blood for a limited duration (< 24 hours). These tests included cytotoxicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, hemocompatibility (hemolysis, thrombogenicity, thromboresistance, and complement activation), and pyrogenicity. No significant adverse findings were noted. All test results demonstrated that the stent was biocompatible and acceptable for its intended use."

In Vivo Animal Tests

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment. For example, findings of maneuverability, performance and pathology information.

Example: "Acute animal studies were conducted to evaluate the performance and safety of the <device name>. Device flexibility, pushability, trackability, stent security, stent strut apposition to the vessel wall, stent symmetry following deployment, and vessel wall injury were evaluated using quantitative coronary angiography. The <device name> met the acceptance criteria and is deemed to be acceptable for clinical use."

Example: "The XYZ stent was evaluated in two separate animal studies at the animal facility of <name of the facility>. Both studies were conducted using experimental protocols that conform to GLP regulations.

The first study was designed to evaluate the potential impact of arterial curvature and stent length on the vascular response to stent implantation. The XYZ stents were provided bare (un-mounted) and the balloon delivery catheter was the XXX balloon. 32 mm stents were implanted in curved segments of porcine coronary arteries, and the arteries were harvested 28 days after implantation. The 28-day morphometric analysis showed expected results in terms of neointimal thickening and injury scores along the stent length. The overall performance of the XYZ stent was acceptable, raising no safety concerns.

In the second animal study, the restenosis rate, characterization of the stent material, and its biological effect in a porcine vascular model were evaluated. For this study, short (9 mm) XYZ stents were premounted on ZZZ balloon catheters using a handcrimping machine. The arteries were harvested at 28 days. The study demonstrated tissue responses consistent with stenting at 28 days after porcine coronary stent implantation.

Quantitative angiographic and histomorphometric analyses confirmed that there were no toxicity concerns over the full range of assessment parameters in aggregate and for sections taken at the proximal, middle and distal portions of the stents."

In Vitro Diagnostic Studies

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment. For example,

- Validation of Cutoff: distinction between positivity and negativity or medical decision limits.

- Sensitivity/Specificity: smallest detectable amount of the analyte in question, proportion of confirmed positive and negative samples tested.

- Interference: any substances that are encountered in specific specimen types or conditions should be tested using the assay system, such as, temperature, time, hemolysis, lipemia, microbial contamination, additional analytes, antibodies or other autoantibodies present, prescription drugs, over the-counter medications, dietary supplements, human anti-mouse antibodies, etc.

- Reproducibility: within run and between-run variations (e.g., the results for all lots and all sites show acceptable precision in all cases.)

- High-Dose Hook effect studies

- Specimen collection and handling conditions

Example: "The limit of detection at a 95% rate was calculated to be <value>. The results for all lots and all sites show the specificity of <#>% (95% confidence limits of <#>% to 100%), based on the correct identification of (#/#) negative samples compared to matched serum specimens, and, a sensitivity of <#>% (95% confidence interval <#> to 100 %) based on the correct identification of #/# positive samples compared to matched serum specimens. The coefficient of variation for inter-site, inter-assay and intra-assay precision ranged between <#> and <#>%. Specimen collection, shipping and storage in <storage system/vehicle> under extreme heat and humidity were shown to exhibit acceptable stability for <#> days. Studies on effect of substances that are encountered in specific specimen types or conditions on the assay system were found to be satisfactory and the critical information is included in the package insert."

Stability/Shelf Life Studies

The general conclusions (e.g., regarding storage conditions, shelf-life, container closure system, shipping, and/or monitoring conditions) derived from the review of any supporting stability studies which figured significantly to Health Canada's decision, should be summarized and accompanied by Health Canada's assessment to the extent possible. Any commitments to provide real-time data, should be mentioned.

Example: "Real-time stability study data submitted supports a 780 day expiry period for <device name> when they are stored under approved storage conditions."

3.4.5 Clinical Effectiveness and Safety

The study designs and results of those studies figuring significantly in Health Canada's decision should be summarized and accompanied by Health Canada's assessment. For example, analysis of device-related investigations conducted, relevant publications in the peer-reviewed scientific literature, clinical studies in special populations (if applicable), description of patient exposure (i.e., extent of a safety database), summary of adverse events during investigational testing (Tabulated summary if possible), post-market actions including incident reports, laboratory findings, safety in special populations, etc. should also be discussed where they figured significantly in Health Canada's decision. The section should conclude with an analysis of clinical effectiveness and safety, including any precautions or contraindications that have been included in the labeling.

For a near-patient *in vitro* diagnostic devices, a summary of investigational tests conducted on the device, simulating expected conditions of use.

If information other than that found in the application (e.g., review from another jurisdiction, recommendation from Expert Advisory Committee, etc.) was evaluated, it should be described along with Health Canada's assessment of the information and its impact on the decision.

If the recommendation is based on the application of a policy or guidance, it should be referenced; if a policy or guidance was deviated from, outline the rationale for the deviation.

If the recommendation is that the licence be issued with terms and/or conditions, the tests to be performed should be described, including the rationale for the decision. A discussion on any limitations of the safety database that require further confirmatory studies (e.g., non-comparative studies, phase II studies etc.) should also be included. Also, address any safety issues to be addressed in post-marketing commitments.

Example: "A multi-center, non-randomized, single-arm prospective clinical trial was conducted to evaluate the safety and effectiveness of the <device name> in patients with single or multiple vessel coronary artery disease who were scheduled to undergo percutaneous coronary intervention because of symptoms of stable or unstable angina pectoris. Twelve sites entered a total of 263 patients (366 lesions) eligible for elective coronary angioplasties who met the inclusion/exclusion criteria. The hypothesis of the study was that the procedural success rate and clinical success rate for the <device name>, were equivalent to objective performance criteria based on contemporary published literature.

The results of the investigational testing study demonstrate that the <device name> is reasonably safe and effective for use in Percutaneous Transluminal Coronary Angioplasty (PTCA) procedures. The procedural success and clinical success rate that were observed in this investigation are equivalent to those reported in similar historical studies of other PTCA catheters that have been published in the medical literature. The rate and type of Major Adverse Coronary Events (MACE) also are similar to those associated with other PTCA catheters. The use of a wire external to the device and the resultant reduced crossing profile, permitted effective lesion dilatation, and did not result in any observed increase in MACE rates or perforations/dissections. The study also demonstrates that the <device name> can be used in either in-stent restenosis or *de novo* lesions with similar safety and effectiveness. These results were confirmed by a separate single-center investigation conducted in Europe and supported by subsequent commercial experience. Thus, the device is reasonably safe and effective for its intended use."

3.4.6 Software Validation Studies

Include the general statement "Software Version 2.1 was validated."

3.4.7 Labelling

The labelling material provided for the <device name> was reviewed and found to meet the requirements of Section 21 of the *Medical Devices Regulations.*

3.5 Risk/Benefit Assessment

Summary of the risk/benefit assessment for the device, including any quality, effectiveness or safety concerns. This should include all factors affecting the risk/benefit assessment, including risks inherent in the use of the device, infectious reagents, a comparison with a licenced device, etc. Strategies for mitigating the risks should be described (e.g., post-market commitments, labeling changes, etc.).

If the product was reviewed under the Priority Review Policy, include a discussion of the rationale for applicability of the policy.

If the licence was issued with terms and/or conditions, include the rationale for this decision.

Example: "The results of *in vitro* testing suggest that the <device name> should perform as anticipated when implanted in human patients. The *in vivo* animal testing evaluated safety and function and met their respective study objectives. The clinical data demonstrated that the device performs as expected with regard to hemodynamic performance and the incidence of conduit-related adverse events.

It is expected that the device will undergo replacement due to pediatric patient growth. It is an interim device that provides the physician with a tool to manage the patient until the patient attains growth to allow consideration of other alternatives for their congenital cardiac repair. The current device alternatives available include patches, valveless conduits, composite prosthetic conduits (mechanical and tissue derived) and human homografts.

The benefits unique to this device include the off-the-shelf availability of small sizes, as compared with homografts, the natural continuity between the valve and conduit, and the ability to use the device without the need for proximal or distal extension.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available or alternative forms of treatment when used as indicated in accordance with the directions for use." [***Link to the package insert and/or the operator's manual for the device***].

3.6 Decision

Include the following statements:

For new licence application: "The application for a New Medical Device Licence complies with the requirements of the *Medical Devices Regulations*, Part 1 and in accordance with Section 36(1)(a), a licence was issued."

For amended licence application: "The application for an Amendment of Device Licence complies with the requirements of the *Medical Devices Regulations*, Part 1 and in accordance with Section 36(1)(b), a licence was issued."

For device licence with terms & conditions: "Based on the Health Canada review of data on quality, safety and effectiveness, Health Canada considers that a post-marketing study will have to be performed on <device name> in order to detect possible rare and unforeseen adverse events, and to ensure that the benefit/risk profile of <the device> is acceptable. Therefore, Health Canada has granted this licence with terms and conditions in accordance with *Medical Devices Regulations*, Section 36(2)."

4 APPLICATION MILESTONES

Include the steps taken within the application process, according to the following **sample table**. With each milestone, include the name and title of the person responsible, and the date of sign off.

Application Milestone	Date
Pre-application meeting	
Request for priority status	
Filed	
Rejection/approval issued by Bureau Director	
Application Received	
Application Validation	
Screening Acceptance	
Review	
Review of additional information	
Level 1 Appeal	
Filed	
Rejection issued by Bureau Director	
Level 2 Appeal	
Filed	
Grant issued by Director General	
Licence Issued	