Health Canada Santé Canada

Examples of clinical evidence requirements for medical devices

Canada

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Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments. Because they do not have force of law, they allow for a flexible approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate 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's equally important to note that Health Canada reserves the right to request information or material, or define terms and conditions not specifically described in this document. This allows us to adequately assess the safety, effectiveness or quality of a medical device. We are committed to ensuring that such requests are justifiable and that decisions are documented clearly.

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Purpose

This document is to be read with the Guidance on clinical evidence requirements for medical devices. It is to help manufacturers and regulatory representatives understand when clinical evidence is necessary to demonstrate the safety and effectiveness of a medical device for its intended use. Detailed examples relating to a variety of medical devices have been provided to enhance understanding.

The *Guidance on clinical evidence requirements for medical devices* outlines the general principles and criteria for clinical evidence that must be submitted for Class III and IV licence applications. The guidance also outlines the clinical evidence that may be requested for certain Class II licence applications and other obligations throughout a device's life cycle.

In particular, the page Submitting clinical evidence outlines the factors that:

- may influence whether device-specific clinical evidence may be required
- would reduce the need for device-specific clinical evidence

Manufacturers are encouraged to consider those factors as they review the examples provided on this page.

Scope

The examples are meant to help manufacturers determine if clinical evidence will be:

- requested for certain Class II licence applications or
- required for Class III and IV licence applications

Manufacturers should bear in mind that these examples are provided for consideration only. They do not bind Health Canada to reviewing an application of a similar nature.

Due to the fast-changing technological environment, this guidance document may be updated periodically to reflect the medical device landscape.

Examples of clinical evidence

Class II medical devices

Example 1: A new licence application for a drug-coated angioplasty balloon is indicated exclusively for treatment "below-the-knee"

In this example, the medical device would target arteries that are below the knee, which are not part of the central cardiovascular system as defined in section 1 of the *Medical Devices Regulations* (Regulations). Thus, this device would be classified as a Class II medical device.

Factors that influenced whether clinical evidence is required	Response
Are similar devices with the same intended use on the market in Canada?	Yes. Similar non-coated balloons are licensed in Canada for "below-the-knee" indications.

Factors that influenced whether clinical evidence is required	Response
Are similar devices with the same product design on the market in Canada?	Yes. Similar drug-coated balloons are licensed for treatment "above-the-knee" but the risk-benefit profile differs for a "below-the-knee" indication.
Is there published clinical literature to support using this device for the proposed indication?	Published clinical literature supports the use of balloon angioplasty for a "below-the-knee" indication. However, there isn't consensus on whether the increased risk of adding a drug coating is justified by a corresponding improvement in patient outcomes.
These new applications **will require** device-specific clinical evidence. Although this is a Class II device, the Regulations enable the Minister to request additional information and samples under section 35 during the application process. In this instance, section 35 would be used to request the submission of device-specific clinical evidence.	

Class III medical devices

Example 1: A conventional bone fixation screw for fractured bony structure or arthrodesis

Factors that influenced whether clinical evidence is required	Response
Is this an established technology?	Yes. Metallic bone screws are devices with established technology. However, the bone screws have been modified. Fenestrations have been created near the tip of the cannulated screw for bone cement injection to enhance screw fixation.
Has the performance of the device been assessed through pre-clinical standardized testing?	Yes. This device has demonstrated equivalent mechanical performance to a comparable licensed screw with the same intended use (the device has been tested for torsional strength, driving torque and axial pullout strength). However, although mechanical performance of the screw can be fully characterized through comparative bench testing, the long-term impact of bone cement on local bone tissue remains uncertain.
The subject screw **is less likely** to require device-specific clinical evidence. However, in certain locations (for example, femoral head or vertebral body, when bone cement is used together with the screw to enhance fixation), the subject screw and the compatible bone cement **will require** device specific clinical evidence.	

Example 2: A mammography system intended for screening and diagnosis of breast cancer using 3-dimensional digital breast tomosynthesis (DBT) alone, without being an adjunct to more clinically established 2-dimensional, full-field digital mammography

Factors that influenced whether clinical evidence is required	Response
Is this a novel or less established device technology than those on the Canadian market?	Yes. The mammography system is not adjunct to a more clinically established 2-dimensional full-field digital mammography.
Can the performance of the device be fully characterized through pre-clinical standardized testing?	No. As DBT is not yet clinically established and data acquisition and performance can vary between manufacturers, a device-specific clinical study is required to assess the sensitivity and specificity of the device in different clinical scenarios.
Will the device be used in various gender-diverse groups across the lifespan?	Further, the mammography system will be used primarily in diverse groups of women. It may also be used (although rarely) to diagnose breast cancer in biological males.
This device **will require** device-specific clinical data.	

Example 3: An intraocular lens (IOL) that incorporates a novel optical design

Factors that influenced whether clinical evidence is required	Response
Is there a marketed comparator device to support the clinical safety and effectiveness?	No, not with the new optical design. IOLs generally have historical comparison referenced, but this is not sufficient if not the same optic.
Is there published literature to support understanding of the device's use and performance?	No. There is no published literature or the literature does not include a sufficient number of patient eyes to allow both clinically relevant and statistically defendable conclusions. Existing investigations have not had sufficient follow-up time to ascertain the frequency and occurrence of known or foreseeable negative impacts.
An appropriately designed, device-specific clinical investigation **will be required** to assess a novel optical design on patient perception including safety, effectiveness and patient satisfaction.	

Example 4: A manufacturer of a medical imaging and treatment planning software wishes to amend their device licence to add a feature to identify the lungs of a patient automatically:

a. using an artificial intelligence (AI)-based algorithm, to assist in radiation treatment planning. AI-based algorithms are not as common in medical imaging as edge detection algorithms, and the health care provider does not have to validate the results before proceeding to the next step in the workflow.

Factors that influenced whether clinical evidence is required	Response
Is this an established technology?	No. While AI-based algorithms are becoming more popular, these algorithms are not yet established and highly sensitive to the data they were trained on. Typically, they need to demonstrate performance in the environment in which they are intended to operate.
Are similar devices with the same intended use and device technology on the market in Canada?	Yes.
Is this a change to current clinical practices associated with using the medical device?	Yes. In this example, the software performs a task that the health care provider would have normally done manually. Results are not validated before continuing to the next step. There is a change to the current clinical practice.
This device licence amendment **will require** clinical evidence.	

b. using an edge detection algorithm, to assist in radiation treatment planning. Edge detection algorithms are very common in medical imaging, and the health care provider must validate the results before proceeding to the next step in the workflow.

Factors that influenced whether clinical evidence is required	Response
Is this an established technology?	Yes. Image analysis software and edge detection algorithms are established technology.
Are similar devices with the same intended use and device technology on the market in Canada?	Yes.
Is this a change to current clinical practices associated with using the medical device?	No. In this example, the software assists in a task that the health care provider would have normally done manually and allows the health care provider to intervene if necessary. There is no change to current clinical practice.
This device licence amendment **will less likely require** clinical evidence.	

Example 5: Expansion of magnetic resonance (MR) conditional labelling claims to include 3.0 Tesla MRI environments, where the passive implantable device might currently only have allowances for use in a 1.5 Tesla MRI environment

Factors that influenced whether clinical evidence is required	Response
Is the technology well understood and can testing establish the impact of the device on the patient?	Yes. Bench testing and numerical simulations can predict the behaviour of the device in the full range of patients and full range of MR environments in which the device will be used.
This device **will less likely require** device-specific clinical evidence.	

Example 6: A general-purpose diagnostic ultrasound system that has well-established modes of operation requests a licence amendment to include additional transducers

Factors that influenced whether clinical evidence is required	Response
Is this a novel or less-established device technology than those on the Canadian market?	No. An established technology would have recognized standards, pre-clinical data, large amounts of literature review, real world data and/or clinical data and has an established benefit-risk profile.
Can the performance of the device be fully characterized through pre-clinical standardized testing?	Yes. Acoustic outputs, patient contact materials, thermal outputs, compatibility and software-based measurement functions demonstrate that this device is safe and effective.
This ultrasound system **will less likely require** device-specific clinical data.	

Example 7: A cosmetic laser indicated for temporary circumferential reduction (body contouring)

Factors that influenced whether clinical evidence is required	Response
Is there a comparator device licensed in Canada?	Yes.
Are the intended use and characteristics of the device the same as for the comparator device?	Yes. The indications for use and detailed treatment parameters (for example, wavelength, power output, spot size, pulse duration, pulse frequency) are identical to the comparator device that has been authorized in Canada. The intended health care practitioner user is the same. The means of delivering the energy is also the same, being a similar user-held and operated hand piece.

Factors that influenced whether clinical evidence is required	Response
Is there clinical literature to support the safety and effectiveness of the device?	Yes. A literature review can be used to support clinical safety and effectiveness if the specific characteristics and features of the subject device and the proposed treatment parameters are identical and if the group studied represents the population in Canada. The literature review must have enough detail on treatment parameters and clinical outcomes to allow Health Canada to assess the validity of the clinical data.
This laser **will less likely require** device-specific clinical data.	

Example 8: The manufacturer wishes to expand the patient population by age or clarify the existing patient population claimed for implantable hearing devices (for example, bone conduction system, cochlear implant)

Factors that influenced whether clinical evidence is required	Response
Are similar devices with the same intended use and device technology on the market in Canada?	Yes.
Is there existing clinical literature to support the addition of new populations?	Yes. The clinical evidence to be provided could be device-specific or only technology-specific depending on the: • requested claim • similarity of the design of the subject device to similar licensed devices in Canada • similar marketed devices internationally for which there is supporting literature with sufficient details on design, assessment and clinical outcomes • risk factors associated with the device and the new claims
If the clinical evidence sufficiently covers these elements, the device **will less likely require** clinical evidence to support the expanded claim.	

Example 9: New applications or amendments to a surgical stapler (linear cutter), including staples

Factors that influenced whether clinical evidence is required	Response
Are similar devices with the same intended use on the market in Canada?	Yes.
Are similar devices with the same product design on the market in Canada?	No. Comparison to a licensed device of a different manufacturer is highly unlikely to be sufficient due to the multifactorial considerations of product design.
Can the performance of the device be fully characterized through pre-clinical standardized testing?	Yes. The safety and performance of these products can often be supported by well-designed, device-specific bench testing, appropriate specifications and test criteria, ex vivo and/or animal studies or appropriate simulation models.
Is this an established device technology?	Yes. Surgical staplers are an established technology with a large amount of clinical evidence. The use and risk profile is known.
Has bench testing been conducted for the device?	Yes. Bench testing is key in determining performance and verifying the failure/risk profile with the proposed modifications, and the expected clinical outcome.
These new applications or amendments **will less likely require** device-specific clinical evidence.	

Class IV medical devices

Example 1: Introduction of a new permanent implant into the heart designed to reduce the risk of thromboembolism

Factors that influenced whether clinical evidence is required	Response
Is the device currently licensed in Canada?	No. The device is not licensed in Canada.
Is the medical device designed for long-term implantation?	Yes. It's a permanent implant.
Is this a novel or less-established device technology?	Yes. This is a new type of implant. The risk of device thrombosis is based on the material and geometric design of the device.
The device **will require** device-specific clinical evidence.	

Example 2: Condition added at time of licensing on a novel trans-catheter aortic heart valve device to monitor post-market safety and long-term effectiveness using a clinical study

Factors that influenced whether clinical evidence is required	Response
Is the device currently licensed in Canada?	Yes. The device is licensed.
Is this a novel or less-established device technology?	Yes. This is a novel or less-established device technology.
Can the performance of the device be fully characterized through pre-market clinical testing?	No. Clinical and durability bench testing data would have been submitted as part of the licence application. These data would have been sufficient to support safety and effectiveness over a period that can reasonably be evaluated pre-market. However, as this is a novel device, longer-term data collected from a larger sample size would also be needed to assess long-term effectiveness. These data would also be necessary to appreciate the incidence rates of possible adverse events, which occur so infrequently that they cannot be evaluated in a pre-market study.
This device **will require** device-specific post-market clinical evidence to monitor safety and long-term effectiveness.	

Example 3: The manufacturer of a cardiovascular device wishes to amend the device licence to:

a. add a different size of the coronary stent. Coronary stents come in a range of sizes. The size of the coronary stents that are currently licensed are 3 mm and 4 mm in diameter. The manufacturer is proposing 2 new sizes: 2.5 mm and 3.5 mm.

Factors that influenced whether clinical evidence is required	Response
Is the device currently licensed in Canada?	Yes. The device is licensed in Canada.
Is this a minor design modification to an existing technology?	Yes. The 3.5 mm size falls between 3 mm and 4 mm, so it can be considered a minor design modification. However, the 2.5 mm stent is outside the current size range of the coronary stents and would be considered a major design modification.

Factors that influenced whether clinical evidence is required	Response
Clinical evidence **will less likely be required** for the 3.5 mm coronary stent. However, for the 2.5 mm stent, it's more likely that device-specific clinical evidence **will be required** because the size to be added is outside of the currently licensed size range.	

b. amend the device licence to change the labelling to allow a decrease in the duration of dual antiplatelet therapy (medication) to be taken following implantation of the device compared to what is typically given, based on current clinical guidelines.

Factors that influenced whether clinical evidence is required	Response
Is the device currently licensed in Canada?	Yes. The device is licensed in Canada.
Is this a change to current clinical practices associated with using the medical device?	Yes. As there's a change to the medications used following implantation, and as these are not in line with current clinical practice, the clinical outcomes could be negatively influenced by a reduction in the length of time the medication is taken.
For the change in medication used with the device, device-specific clinical evidence **will be required** because of the impact to the therapeutic outcomes that may occur.	

Sex and gender-based analysis Plus (SGBA Plus) considerations

Example 1: A new licence application for a novel permanently implanted device intended for electrical stimulation of the parasympathetic nervous system for treatment of patients with heart failure

Factors that influenced whether clinical evidence is required	Response
Are similar devices on the market in Canada?	No. Similar devices are not licensed in Canada.
Is the medical device designed for long-term implantation?	Yes. It's a permanent implant.
Is the device used in both male and female populations?	Yes. Sex differences in cardiac electrophysiology are reported in the literature.

Factors that influenced whether clinical evidence is required	Response
Is this a novel or less-established device technology?	Yes. This is a novel implant and alternative devices are not licensed.
This device **will require** device-specific clinical evidence. The study population should reflect the diversity of the population in Canada. It should represent all sexes, ethnic subgroups and racial backgrounds.	

Example 2: A licence application for a pulse oximeter with a novel sensor that differs from currently licensed sensors in electrical and design characteristics

Factors that influenced whether clinical evidence is required	Response
Are similar devices on the market in Canada?	Yes. Pulse oximeters are licensed in Canada.
Is this a novel or less-established device technology?	Yes. The pulse oximetry sensor differs sufficiently from currently licensed sensors that it's impossible to establish equivalency to licensed devices.
Is the device used on diverse groups of patients with different skin pigmentation?	Yes. Pulse oximeter is used on a wide range of the Canadian population, including those with a range of skin pigmentations.
Is there published clinical literature suggesting that effectiveness is impacted by skin pigmentation?	Yes. Published clinical literature suggests that measurement accuracy may be diminished by darker skin pigmentation.
Are there clinical consequences if the device is not accurate?	Yes. An inaccurate pulse oximeter would affect treatment decisions for the patient.
Are there technical standards that specify test requirements for different skin colours?	No. However, international standards state that subjects should vary in their physical characteristics to the greatest extent possible and their skin colour should be described. This description should be noted in the labelling.
The device will require device-specific clinical data with a specific SGBA Plus to demonstrate device effectiveness over a range of skin pigmentations representative of Canada's diverse population. Manufacturers are encouraged to perform an SGBA Plus and refer to the United States Food and Drug Administration pulse oximeters guidance document as needed.	