Guidance for Industry

Guidance for the Submission of Premarket Notifications for Photon-Emitting Brachytherapy Sources

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U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Radiological Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to name, office, mail stop, address. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Robert Phillips, Ph.D., at (240) 276-3666 or email RobertAPhillips@fda.hhs.gov.

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Guidance[1] for the Submission of Premarket Notifications for Photon-Emitting Brachytherapy Sources

I. Purpose

The purpose of this document is to provide a detailed description of the information that should be included in a premarket notification (510(k)) for a photon-emitting Brachytherapy Source submitted to the Center for Devices and Radiological Health (CDRH). This information is an elaboration of the general requirements contained in 21 CFR 807.87.

II. Scope

This document is applicable to superficial and interstitial photon-emitting Radionuclide Brachytherapy Sources as defined in 21 CFR 892.5730.

> "A radionuclide brachytherapy source is a device that consists of a radionuclide which may be enclosed in a sealed container made of gold, titanium, stainless steel, or platinum and intended for medical purposes to be placed onto a body surface or into a body cavity or tissue as a source of nuclear radiation for therapy."

Brachytherapy sources are currently in Class II and require premarket notification (510(k)) and an agency determination of substantial equivalence prior to marketing. The product code currently used to identify this device is KXK. This guidance covers all sources intended for use in brachytherapy but does not cover sources intended for use in the cardiovascular system for the prevention of restenosis. Some sources may also need approval from the Nuclear Regulatory Commission or an Agreement State department of radiation control prior to marketing.

The principal components of current brachytherapy sources are the radioactive material, sometimes adsorbed or plated onto a substrate, and its encapsulation.

[1] This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance is applicable to 510(k)s for new photon-emitting brachytherapy sources and modifications to existing brachytherapy sources and their components that have a significant influence on safety or effectiveness.

III. Background

In the last few years, a number of legislative changes relating to the authority of the agency have occurred. These changes have resulted in the adoption of new regulations and administrative procedures by CDRH, which affect the 510(k) process. The Safe Medical Devices Act of 1990 (SMDA) has resulted in new Good Manufacturing Practice (GMP) regulations requiring pre-production design controls, and several administrative requirements (Truthful and Accurate statements, Summaries of Safety and Effectiveness, and Statements of Indications for Use) have been added. The Food and Drug Administration Modernization Act (FDAMA) of 1997 and a re-engineering effort have resulted in the development of a new 510(k) paradigm that incorporates alternative approaches to demonstrating substantial equivalence in premarket notifications. These approaches are intended to facilitate the marketing clearance of devices for which recognized standards exist, and for cases in which the new device is a modification of a previously cleared product.

A. The New 510(k) Paradigm

On March 20, 1998 CDRH issued a document entitled "The New 510(k) Paradigm - Alternative Approaches to Demonstrating Substantial Equivalence in Premarket Notifications". This document is available on the CDRH web site (http://www.fda.gov/cdrh/ode/parad510.html). In addition to the traditional 510(k), this document describes two alternatives, the "Special 510(k): Device Modification" and the "Abbreviated 510(k)".

1. Special 510(k)

The Special 510(k) is based on the requirement that manufacturers establish design controls in accordance with the SMDA and 21 CFR 820.30. A manufacturer uses the FDA guidance document entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" to decide if a device modification could be implemented without submission of a new 510(k). If a new 510(k) is needed, and if the modification does not affect the intended use of the device or the basic fundamental scientific technology, conformance with design controls may form the basis for clearing the application. Under this option, a manufacturer who is intending to modify a legally marketed Class II device would conduct the necessary verification and validation activities to demonstrate that the design output of the modified device meets the design requirements. Once the company has ensured the satisfactory completion of this process through a design review, a Special 510(k) may be submitted. While the basic content requirements for the submission are the same, this type of submission should also reference the cleared 510(k) and contain a "Declaration of Conformity" with design control requirements. In the Special 510(k) the manufacturer has the option of using a third

party to assess conformance with design controls (refer to the paradigm document for details). Special 510(k)s are processed by the Office of Device Evaluation within 30 days of receipt.

2. Abbreviated 510(k)s

The Abbreviated 510(k) is based on the use of conformance to voluntary standards or a guidance document in place of data review as the means by which the safety and effectiveness of Class II devices can be assured. A guidance document on the use of standards, "Use of Standards in Substantial Equivalence Determinations" (www.fda.gov/cdrh/ode/guidance/1131.pdf) was issued in March of 2000. This guidance established three methods for using voluntary standards in place of data in a 510(k). These were: the submission of a Declaration of Conformity to an FDA-recognized standard, a statement that a device conforms (or will conform prior to marketing) to an FDA-recognized standard (to be used where statements have been previously used), and a statement that the device conforms (or will conform) to a standard that is not yet recognized by FDA. In the last case there is less assurance that the non-recognized standard will be acceptable in meeting 510(k) requirements and the sponsor is responsible for providing sufficient justification that the non-recognized standard is suitable for its purpose. In addition to the required elements of a 510(k) as described in 21 CFR 808.87, Abbreviated 510(k) submissions should include information that describes how conformance to one or several voluntary standards, have been used to address risks associated with the device. A third party may be used to assess conformance with these standards (refer to the paradigm document for details). The review of abbreviated 510(k)s is intended to be more efficient since they are not required to contain the experimental (test) data from which conformance is determined.

B. Applicable Guidance and Standards for Photon-emitting Brachytherapy Sources.

1. ANSI N43.6-1997 Classification of Sealed Radioactive Sources
2. ISO 2919 Sealed radioactive sources—General requirements and classification .
3. A New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications (http://www.fda.gov/cdrh/ode/para510.pdf)
4. Use of Standards in Substantial Equivalence Determinations (http://www.fda.gov/cdrh/ode/guidance/1131.pdf)
5. National Institute for Standards and Technology (NIST) calibration standards for specific radionuclide and source encapsulation. (http://ts.nist.gov/ts/htdocs/230/233/calibration/users/index.html)

IV. Information to be Submitted in a Premarket Notification

A. General

1. Name and address of manufacturer
2. Establishment registration number (if not available, registration application should be submitted)
3. Name, title, phone number, fax number and E-mail of contact
4. Trade name, model number, and common name of device
5. Type of 510(k) submission (special, abbreviated or traditional)
6. Classification and class of device (21 CFR 892.5730, Class II), and product code (90-KXK)
7. Intended use (general purpose of device per 21 CFR 892.5730)

B. Administrative Information

1. 510(k) Summary of Safety and Effectiveness or Statement (see 21 CFR 807.92 and 807.93) (see Appendix 1)
2. FDA Indications for Use Form (specific diagnostic or therapeutic use of device, i.e**.** the anatomical region and/or disease/condition which the device is intended to diagnose or treat) (see Appendix 2)
3. Truthful and Accurate Statement (see 21 CFR 808.87(j)) (see Appendix 3)
4. Declarations of Conformity or Statements of conformance to voluntary standards (Abbreviated 510(k) only) (see Appendix 4)
5. Declaration of Conformity to Design Controls (Special 510(k) only)

C. Source Material Information:

The submission should contain the following information about the source radionuclide:

1. Identification of the principle radionuclide in the source
2. Identification of all other radionuclides/contaminations in source with their percentages
3. Specification of all the important physical properties for each of the radionuclides within the source including at least:
   a. half-life (or lifetime) and units
   b. decay modes
   c. branching ratios
   d. energies of all radiation present with units

D. Source Design/Encapsulation Information:

The submission should provide the following source design information:

1. Identify the source encapsulation material and the internal composition of the substrate. Specify how the source encapsulation (and substrate) affect the output, e.g., is bremsstrahlung significant during storage of sources or treatment of patients (If yes specify it.). Does the source structure modify the photon spectrum in any way that could affect the dosimetry calculations?
2. Specify the source configuration.
3. Provide a complete set of engineering drawings/diagrams of the source and encapsulation including the physical dimensions of source.
4. Specify if the source meets the ANSI N43.6-1997 or ISO 2919 standard for sealed radioactive source-classification. If yes, provide the classification code and a Declaration of Conformity or statement of conformance to the standard.
5. A copy of the sealed source certificate issued by the Nuclear Regulatory Commission, an agreement state, other responsible authority, or a statement that such a certificate will be acquired prior to introducing the source into commerce.

E. Source Output Information

Source output information should provide the following:

1. The physical quantity (with associated units) used to specify the source output (air-kerma strength, "apparent " activity[2], other)
2. The accuracy (or uncertainty at a specified confidence level) of the source output value supplied to the customer.
3. The method of specifying each seed if multi-seeds are used in a sourcetrain.
4. How the output of seeds is measured and how the output of a multi-seed sourcetrain is measured.
5. The measured dose distribution and isodose curves around the source. Describe how the dose distribution was measured. Were calculational techniques (e.g. Monte Carlo) used to confirm the dose measurements? If yes, give the name and version of code and provide information on what verification and validation procedures were done to ensure that the use of the code is correct for this application, How were the measured or calculated dose rates normalized to the source output as described in (4) above?

F Manufacturing Process Information

[2] "Apparent" Activity is defined as the ratio of radiation output of the encapsulated source, in terms of air-kerma strength for gamma emitting nuclides, to the product of the energy needed to produce an ion pair and a "constant" called the exposure rate constant (gamma). Note: The apparent activity is not the same as the "true" (contained) activity of the source.

1. Provide a description of your in-house calibration system. How do you assure that traceable calibrations are transferred to each manufactured source? Note: the calibration should be traceable[3] to a national standard maintained by the (NIST) or other equivalent national standard. Describe how this traceability is achieved.
2. Describe the quality system used to ensure that all the sources produced/assembled meet the manufacturing specifications.
3. Identify any limitations on your source that the customer should be aware of.

G. Labeling Information

The labeling for the device in the submission should contain:

1. The indications for use of the device (source), e.g. is the source limited to specific types of treatment.
2. Specification on whether the source is intended for single or multiple use. If it is intended for multiple use, recommendations for cleaning and disinfecting the source.
3. Any contraindications, warnings, precautions associated with the device (including a prescription statement).
4. A cross-sectional diagram of the source, including internal components, with dimensions.
5. Listing of the physical properties of the source including:
   a. all other radionuclides/contaminations with their percentages,
   b. the half-lives (or lifetimes) of all radionuclides/contaminations with units,
   c. the types of radiation present (e.g., photon, beta), including any fluorescent x-ray that may be present.
   d. the energies of all radiations present, and the branching ratios of all radiations present.
6. Recommended useful "shelf life" of source.
7. How the seed is intended to be "implanted" or used (e.g., HDR, implanted through needle, hand delivered via catheter).
8. A description of any special leak test procedures the customer should use before implanting the source or for routine monitoring the source.
9. Recommended methods for sterilizing the source prior to use.
10. Recommended methods for disposing of used or unused sources.
11. Identification of any limitation on your source that the customer should be aware.
12. The dosimetric properties of the brachytherapy source/system. Provide sufficient information on the dosimetry of the source to be able to determine the dose delivered to the prescribed

[3] Traceability of the in-house reference standard used to characterize a brachytherapy source calibration system used in the manufacturing process shall meet one of the two following criteria:
(1) the transfer standard is directly calibrated at the NIST; or
(2) the transfer standard is calibrated at an accredited laboratory which has participated in a proficiency test with NIST for that model source and the results of the proficiency test were within the limits specified in the accreditation criteria.
In both cases it is expected that the transfer standard will be used to characterize the manufacturing source calibration system and that there is a routine quality control program in place to ensure that the manufacturing source calibration system is operating within statistically expected limits.

treatment volume at any point within the treatment volume. Provide the following information in the labeling:

a. What dosimetric model(s) (or mathematical algorithm) is recommended for determining patient dose from the source?
b. Give recommended values for each parameter in the dosimetric model(s) for the source described in this submission.
c. The value of the specified source output , with associated units, at the time of calibration, and the national standard to which the measurements are traceable.
d. The reference time of the calibration.
e. The source should be specified in terms of air-kerma strength. If, in addition, the source output is specified in terms of apparent activity (or its equivalent), provide the conversion factor from apparent activity, or other quantity used, to air-kerma strength.
f. Provide at least two (2) independent determinations of the values of the physical parameters used in the dosimetric model(s) (e.g., see recommendations in Medical Physics[4]).
g. Provide isodose curves of the dose (rate) along the transverse axis of the source(train) from 90 to 10% of the maximum dose (rate). Also, provide the absolute dose (rates) that occur along a line perpendicular to the source axis, through the maximum dose point, for the same conditions.

13. Recommended procedure that that the user can employ to verify that the source output is within the uncertainty stated on the label.

[4] Williamson, Jeffrey, et. al., Dosimetric prerequisites for routine clinical use of new low energy photon interstitial brachytherapy sources, Medical Physics 25 (12) (1998) 2269

Appendix 1

510(k) Summary/Statement Certification

Re: K_____

CHECK ONLY ONE:

☐ **510(k) Summary**. Attached is a summary of safety and effectiveness information upon which an equivalence determination could be based.

☐ **510(k) Statement**. I certify that, in my capacity as

_____

of _____(company), I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61.

_____

[Signature]*

_____

[Typed or Printed Name]

_____

[Date]

* Must be signed by a responsible person of the firm required to submit the premarket notification (e.g., not a consultant for the 510(k) submitter).

Appendix 2

Indications for Use Form

Page___of

510(k) Number (if known):

Device Name:

Indications For Use:

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

_____ _____ _____ _____ _____ _____

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use___ OR Over-The-Counter Use
(Per 21 CFR 801.109)

Appendix 3

PREMARKET NOTIFICATION TRUTHFUL AND ACCURATE STATEMENT

(as required by 21 CFR 807.87(j))

I certify that, in my capacity as _____ of ____ _____(company name), I believe, to the best of my knowledge, that all data and information submitted in this premarket notification is truthful and accurate and that no material fact has been omitted.

_____ _____

(Signature)* *(Date)*

_____ _____

(Typed Name) *(510(k) number)*

* Must be signed by a responsible person of the firm required to submit the premarket notification (e.g., not a consultant for the 510(k) submitter).

Appendix 4

Voluntary Standards

1. Declaration of Conformity (for Retrospective Certification of Production Models only)

Reviewers will rely on a declaration of conformity to the recognized consensus standards if the declaration:

a. Identifies the applicable recognized consensus standards and specifies those that were met;

b. Specifies, for each consensus standard, that all requirements were met, except for inapplicable requirements or deviations noted below;

c. Identifies for each consensus standard any way(s) the standard may have been tailored or modified for application to the device under review, e.g., identifies which of an alternative series of tests were performed;

d. Identifies, for each consensus standard, any requirements that were not applicable to the device;

e. Specifies any deviations from each applicable standard that were applied (e.g., deviations from international standards which are necessary to meet U.S. infrastructure conventions such as the National Electrical Code (ANSI/NFPA 70));

f. Specifies what differences exist, if any, between the tested device and the device to be marketed and justifies the use of test results in these areas of difference; and

g. If a test laboratory or certification body was employed, provides the name and address of each laboratory or certification body that was involved in the determining the conformance of the device with the applicable consensus standards and a reference to any accreditations of those organizations.

2. Statement of conformity (prospective certification)

In certain circumstances, the manufacturer may not able to provide a Declaration of Conformity to a voluntary standard(s), usually because a production line product has not yet been tested or is not able to be tested. Under these circumstances, a statement(s) that the conditions of the standard(s) will be met prior to marketing the device is acceptable. When this is done, the statement should contain the same information as is needed in a Declaration of Conformity, but the statement should be written in the future tense.