Guidance for Industry and for FDA Reviewers/Staff

Guidance on 510(k) Submissions for Keratoprostheses

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

Intraocular and Corneal Implants Branch
Division of Ophthalmic Devices
Office of Device Evaluation

Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Ms. Ashley A. Boulware, HFZ-460, 9200 Corporate Blvd., Rockville, MD 20850. 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 Ms. Ashley A. Boulware at (301) 594-2053 or by electronic mail at (aab@cdrh.fda.gov).

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I. Introduction

A. Scope

Scope - This guidance document serves as a special control for the regulation of temporary and permanent keratoprostheses through the submission of premarket notifications (510(k)s). This guidance does not pertain to devices intended for use in patients with non-opacified corneas.

This guidance document represents the agency's current thinking on keratoprostheses. 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.

B. Device Description

Name:	Temporary or Permanent Keratoprosthesis
Class:	886.3400 (II)
Panel:	Ophthalmic (OP)
Procode:	MLP (temporary); HQM (permanent)

C. Definitions/Intended Uses

Keratoprosthesis -
A device intended to provide a transparent optical pathway through an opacified cornea, either intraoperatively or permanently, in an eye which is not a reasonable candidate for a corneal transplant.

Temporary keratoprosthesis -
Keratoprosthesis used intraoperatively to aid in visualization of ocular structures. This device is intended to be removed following surgery.

Permanent keratoprosthesis -
Keratoprosthesis which is implanted permanently to allow the transmission of light through an opacified cornea.

II. Biocompatibility Testing

A. General

The general requirements specified in FDA's Office of Device Evaluation (ODE) Guidance Memorandum #G-95 apply, with the particular recommendations listed below. All tests should be performed on the finished product as marketed. The test methods specified below are suggested methods. Alternative methods are acceptable if appropriately validated. The omission of any testing should be justified with a valid scientific argument/rationale.

B. Extracts

In tests that are conducted on material extracts, testing should be conducted with two different extractants, one polar, and one nonpolar, except where a given extract is inappropriate (e.g., certain cytotoxicity protocols).

C. Biocompatibility Tests

For all materials, the following biocompatibility testing should be performed:

1. Cytotoxicity -

Cytotoxicity should be carried out in accordance with the requirements of ISO 10993-5 (Biological evaluation of medical devices - Part 5: Tests for cytotoxicity - *in vitro* methods).

The following cytotoxicity tests may be used:

Test	Desired Result
Agar Diffusion Test (Direct Contact)	Non-cytotoxic
Agar Diffusion Test (Extracts)	Non-cytotoxic
Inhibition of Cell Growth	Non-inhibitory
MEM Elution	Non-cytotoxic

2. Genotoxicity -

Testing for genotoxic potential should be conducted using two extractants as outlined in Annex D of ISO/DIS 11979-5 (Optics and Optical Instruments - Intraocular Lenses - Part 5: Biocompatibility), in accordance with ISO 10993-3 (Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity). While ISO/DIS 11979 is a set of standards for intraocular lenses, the referenced methodologies are appropriate for keratoprostheses.

The results should show the material to be non-genotoxic. Otherwise, additional genotoxicity and/or carcinogenicity testing will be necessary.

3. Maximization Sensitization Test -

Testing for sensitization potential should be conducted as outlined using two extractants as outlined in Annex E of ISO/DIS 11979-5, in accordance with ISO 10993-10 (Biological evaluation of medical devices - Part 10: Tests for irritation and sensitization).

The results should demonstrate a lack of sensitization potential.

4. Intramuscular Animal Implantation Test -

This test should be performed in order to demonstrate the tissue tolerance of the test material. Testing should be conducted in accordance with Annex F of ISO/DIS 11979-5.

The results should demonstrate tolerance of the tissue material.

5. Ocular Implantation Test -

This test is performed in order to demonstrate the tolerance of the test material after implantation into the animal eye. Testing should be conducted in accordance with Annex F of ISO/DIS 11979-5.

The results should demonstrate that the test material is well tolerated after implantation into the animal eye.

FDA will consider requests for waivers from the ocular implantation test, provided that:

a. the sponsor provides a valid scientific rationale for omitting the test;

b. the material is chemically identical to a material that has been proven safe and effective as an implant in the human eye (e.g., certain polymethylmethacrylates (PMMAs)); and,

c. the material is derived from the same source as a material proven safe and effective as an implant in the human eye.

6. Chemical Testing -

For silicone materials, the composition of the basic formulation should have any volatile elements (molecular weight less than 1000) reduced to not greater than 1.0 wt% by gravimetric method to minimize potentially leachable compounds.

For PMMA and other polymers, the level of residual monomers should be no greater than 1.0 wt%, determined for the finished keratoprosthesis using an exhaustive extraction method with an appropriate solvent used to swell the polymeric material.

7. Test of Extractables and Hydrolytic Stability -

This test need not be performed for temporary keratoprostheses.

Keratoprostheses materials should be evaluated for monomer content, molecular weight, and identification and quantification of degradation products following hydrolytic aging. Annex A of ISO/DIS 11979-5 describes a test method which may be used to perform this test.

FDA will consider requests for waivers from this test if the material has a well-established record of use in the scientific literature as an ocular implant (e.g., as an intraocular lens).

8. Dimensions and Surface Quality -

All keratoprostheses should be essentially free from pits, scratches, cracking and crazing at a minimum of 6X magnification. The edges should appear smooth and free of burrs and flash when inspected at 6X magnification. The overall dimensions of the keratoprosthesis should be within ±10% of the design nominal.

III. Optical Testing

A. General

All tests should be performed on the finished product as marketed. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated.

B. Dioptric Power

Permanent Keratoprostheses
The sponsor should demonstrate the accuracy of the dioptric power of the keratoprosthesis. The tolerance on the labeled power should be within ±2.0 D. The power should be included in the labeling.

Temporary Keratoprostheses
The sponsor should provide the expected field of view and magnification. This information should also be included in the labeling.

Determination of power may be performed according to the methods outlined in Annex A of ISO/DIS 11979-2 (Optics and optical instruments -- Intraocular lenses -- Part 2: Optical properties and test methods). These methods may not be adequate for devices with large amounts of spherical aberration or those of negative powers. Sponsors should develop methods appropriate to the design of their devices.

IV. Sterility Testing

A. General

The recommendations for sterilization outlined in FDA's ODE Guidance Memorandum #K90-1 should be evaluated for sterile devices. Permanent keratoprostheses should be provided sterile. Whenever possible, the device should be sterilized in its final container. Temporary keratoprostheses may be provided non-sterile. However, if the device is provided non-sterile, FDA's ODE Guidance "Labeling of Reusable Medical Devices for Reprocessing in Health Care Facilities: FDA Reviewer Guidance" should be consulted and pertinent issues identified and addressed.

B. Validation of Sterilization Method

The method used to sterilize the device should be validated as appropriate for the specific sterilization method. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated.

1. Steam Sterilization -

Validation of steam sterilization can be carried out in accordance with the requirements of ANSI/AAMI/ISO 11134-1993 (Sterilization of health care products -- Requirements for validation and routine control -- Industrial moist heat sterilization).

2. Ethylene Oxide (EO) Sterilization -

Validation of EO sterilization can be carried out in accordance with the requirements of ANSI/AAMI/ISO 11135-1994 (Medical devices -- Validation and routine control of ethylene oxide sterilization).

a. EO residual testing can be carried out in accordance with ISO 10993-7 (1995) (Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals) and the draft AAMI TIR (Technical Information Report) for ISO 10993-7. As described in paragraph 4a., since keratoprostheses are not intraocular lenses, the limit for residual ethylene oxide should be pro-rated on the basis of the mass of the device, with the mass of an intraocular lens taken as 20 mg.

   The following modifications should also be implemented:

   - The procedure should consist of a solvent exhaustive extraction or a headspace exhaustive extraction.

     Note - Sponsors should choose a solvent that adequately swells or dissolves the keratoprosthesis material to facilitate extraction of the EO molecules. A headspace method may be used if it has been validated to demonstrate that the extraction is as exhaustive as a solvent method. Alternatively, a sponsor may demonstrate the relative efficiency of an extraction method and adjust the internal release specifications accordingly.

   - The ethylene chlorohydrin (ECH) residue in keratoprostheses should not exceed 2.0 µg ECH per device per day, not to exceed 5.0 µg per device.

     Note - Ethylene glycol residues should be sufficiently controlled by the limits set for EO and ECH residues.

b. Alternatively, the methods described in AAMI ST29-1988 (Recommended practice for determining residual ethylene oxide in medical devices) may be used with the following specified limits:

Residue	Limit
Ethylene oxide	25 ppm
Ethylene chlorohydrin	25 ppm
Ethylene glycol	500 ppm

3. Radiation Sterilization -

Validation of radiation sterilization should be carried out in accordance with the requirements of ANSI/AAMI/ISO 11137 (Sterilization of health care products -- Requirements for validation and routine control -- Radiation sterilization).

V. Packaging and Labeling

1. Packaging -

The packaging is intended to provide adequate protection to the keratoprosthesis from damage during shipping and to maintain the sterility of the device for the duration of its shelf life. Therefore, the following information should be submitted:

a. A description of the packaging, including the packaging materials and the configuration of the final packaged product should be provided.

b. The sponsor should demonstrate that the package maintains the sterility of the device for the duration of the proposed shelf life. A validated seal integrity test in combination with a microbial barrier test (dust drum method, if validated) or a validated whole package physical integrity test should be performed on the finished product before and after aging. Examples of such testing may be found in ISO 11607 (Packaging for terminally sterilized medical devices).

FDA prefers real-time aging be performed for establishing shelf life; however, accelerated aging up to 5 years may be acceptable for device materials with a history of use in ocular implants (e.g., polymethylmethacrylate (PMMA)) and for package materials with a history of use in similar sterilization conditions (e.g., Tyvek pouches sterilized with 100% EO).

2. Labeling -

The labeling for the keratoprosthesis should contain the following information:

- Name of the manufacturer
- Trade name of the product
- A description of the materials and diagram (including top and side views) of the device, which contains its dimensions
- Dioptric power (for permanent keratoprostheses)
- Field of view and magnification (for temporary keratoprostheses)
- Lot/batch number

- Indications for use
- Instructions for use
- Clinical results (including adverse events)
- Warning that the device is sterilized until opened (for permanent and sterile temporary keratoprostheses)
- Precautions to be taken for handling and safe use
- Statement that the device is for single use only (for permanent and sterile temporary keratoprostheses)

Definitions provided in FDA's ODE Guidance Memorandum #G91-1 should be referenced when necessary. The labeling requirements described in 21 CFR Part 801 also apply.

IV. Clinical Investigation

Clinical data are needed in each 510(k) for a permanent keratoprosthesis to confirm the clinical performance. Clinical data are not needed for temporary keratoprostheses. Permanent keratoprostheses are considered significant risk devices, and clinical investigations performed in the United States must take place under an investigational device exemption (IDE). The general requirements described in 21 CFR Part 812 apply to the clinical investigations of keratoprostheses.

Recommended protocol elements may be found in Appendix A.

Appendix A
(Informative)

A.1 General

The following are important elements of a clinical protocol which will assist the sponsor in collecting sufficient, relevant and appropriate data to provide safety and effectiveness information. This information will be included in the labeling for permanent keratoprostheses to provide effective directions for use and to better inform physicians and patients of the relative risks and benefits of these devices.

A.2 Intended Population

The clinical protocol should define the intended population for the device through inclusion and exclusion criteria. For most keratoprostheses, this population will be subjects for whom a corneal transplant is not an option. Sponsors should be advised that the analysis of risks versus benefits will be different for other subject populations and additional protocol elements may be necessary.

A.3 Number of Subjects

The purpose of this investigation is to provide safety and effectiveness information for inclusion in the product labeling. These devices are most often used in a population where a keratoprosthesis is the only remaining option. Since this population is likely to be small, the number of subjects suggested for the clinical investigation is not based on a statistical evaluation, but is a recommendation likely to provide sufficient data for inclusion in the labeling.

The clinical investigation should include a minimum of 20 subjects. The study design should allow for subjects lost to follow-up during the investigation. Sponsors are advised that any extraordinary claims will require the calculation of an appropriate sample size sufficient to support the specific claim.

A.4 Duration of the Clinical Investigation

The follow-up duration of the clinical investigation should be at least one year.

A.5 Reporting Periods

As a minimum, the protocol should specify the following postoperative reporting forms:

Form 0:	Preoperative/Operative
Form 1:	1-3 days postoperatively
Form 2:	30-60 days postoperatively
Form 3:	90-120 days postoperatively
Form 4:	150-210 days postoperatively
Form 5:	330-420 days postoperatively

Unscheduled visits and the procedures to capture adverse events that may occur between reporting forms should be addressed in the investigational protocol.

A.6 Data Analyses

A.6.1 Adverse Events

Any undesirable clinical occurrence in a subject, whether considered to be device related or not, should be reported. Adverse events may occur intraoperatively or postoperatively.

A.6.2 Outcomes

Complications and adverse events are the primary safety outcomes to be evaluated. All complications and adverse events and their rates of occurrence should be reported. Visual acuities should be collected and analyzed, but it is recognized that visual acuity itself may not be the primary success criterion for effectiveness.

If a secondary device is implanted (e.g., a glaucoma drainage device), the device should be clearly identified and the outcomes data should be stratified by the presence or absence of the secondary device.

Dataline listings should be provided for all subjects.