MANUFACTURING/CHEMISTRY

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MANUFACTURING/CHEMISTRY APPENDICES

MANUFACTURING/CHEMISTRY

I. Introduction:

This section of the guidance outlines the types of manufacturing/ chemistry data requirements that should be minimally met in order to demonstrate the substantial equivalence of a daily wear plastic contact lens in terms of safety and effectiveness to a legally marketed daily wear plastic contact lens. Daily wear contact lenses made from materials other than plastics (e.g., collagen, gelatin etc.) may raise new types of safety or effectiveness questions than the predicate device and, therefore, require a premarket approval (PMA) application.

II. Nomenclature and Classification of Contact Lens Plastic Materials:

A. Nomenclature for Nonproprietary Names:

All 510(k) applications for daily wear contact lenses should include a proprietary name (i.e., trade name) for the finished contact lens and a nonproprietary name (hereafter referred to as the "generic name") for the contact lens material. Because CDRH will not accept an application for a daily wear lens without a USAN, a 510(k) should not be submitted until the applicant has either (1) received a letter of authorization from the USAN Council establishing the generic name for the material or (2) has appropriate evidence to conclude that the lens material falls within an existing USAN.

The USAN Council is a private organization sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention, Inc. (USP), and the American Pharmaceutical Association (APA) that assists manufacturers by assigning and publishing generic names and chemical compositions for drug compounds and other medical products that may be regulated by FDA. FDA began its participation in the USAN Council in 1967. The decades of close association between the USAN Council and FDA were strengthened in 1984 when FDA announced that it would recognize and use USAN Council approved designations as established names for labeling and advertising for designated products in the United States. More than 70 generic names for contact lens materials have been assigned by the USAN Council. Generic names assigned by the USAN Council have been widely used by practitioners, manufacturers, and regulatory bodies throughout the world. FDA remains an active member of, and consultant to, the USAN Council.

For purposes of assigning a generic name, the USAN Council uses the following three-part code: (Prefix)(-Stem)(Series Suffix).

1. Prefix: The prefix is a unique and specific designation assigned by the USAN Council that precedes the stem in assigning a parent generic name to a contact lens material. The prefix is the critical designation that distinguishes one lens material from the other within the same generic

class (i.e., hydrophilic or hydrophobic). The prefix is based on repeating monomer units including crosslinking agents.

Additives such as color additives, ultraviolet (UV) absorbers, initiators, catalysts, and fillers are excluded for the purpose of nomenclature.

2. Stem: The stem is a generic term that identifies the material as a hydrophilic or hydrophobic plastic lens material. The two stems used are (1) "-filcon" which is affixed to the prefix of hydrophilic lens materials which have a water content $\geq$10%, and (2) "-focon" which is affixed to the prefix of hydrophobic lens materials which have a water content of <10%. The stem terms "-filcon" and "-focon," established and used by USAN, have been adopted for use in international standards establishing consistent contact lens nomenclature for these terms throughout the world.

3. Series Suffix: The series suffix is an optional capital letter (e.g., A, B, C, etc.) assigned by the USAN Council when the original ratio of repeating monomers within the parent lens polymer have been altered to change physicochemical properties of the parent lens material. These modified lens materials are related to the parent material in that they are comprised of the same repeating monomeric units formulated, however, in different proportions or ratios. The capital letter "A" is generally the suffix given for the original parent material, and subsequent polymer modifications are designated by use of successive capital letters in the alphabet (e.g., B, C, D, etc.) The series suffix is unnecessary when there is a single unique mixture of monomers.

The following are examples of generic names assigned by the USAN Council to contact lens materials:

Examples	(Prefix)	(-Stem)	(Suffix)	USAN
Hydrophilic Lens	(delta)	(-filcon)	(A)	= deltafilcon A
Hydrophobic Lens	(pasi)	(-focon)	(C)	= pasifocon C

The name selection process for a USAN should be initiated when the lens material enters the clinical investigation stage. Requests and proposals for a USAN should be addressed to:

United States Adopted Name Council
American Medical Association
515 North State Street
Chicago, Illinois 60610
(312) 464-4046

In the interest of uniformity, the chemical name for the component of the lens material should be in conformance with the corresponding Chemical Abstracts Index name as employed by the American Chemical Society.

B. Classification of Lens Materials:

Daily wear plastic contact lenses are classified into soft (hydrophilic) and hydrophobic plastic contact lenses depending on their water content. Soft (hydrophilic) plastic contact lenses are defined as lenses having a water content ≥10% by weight at ambient temperature (e.g., 23±2°C). Lens grouping for soft (hydrophilic) plastic contact lenses are categorized into four groups as noted in item 1. Hydrophobic plastic contact lenses are defined as lenses made from materials having a water content of <10% by weight at ambient temperature (e.g., 23±2°C), and are categorized into four groups as noted in item 2:

1. Soft (Hydrophilic) Material Groups ("-filcon"):

Group	Description
I	Low Water Content (<50%), Nonionic*
II	High Water Content (≥50%), Nonionic
III	Low Water Content (<50%), Ionic**
IV	High Water Content (≥50%), Ionic

*Having an ionic content of ≤1% mole fraction at pH = 7.2.

**Having an ionic content of >1% mole fraction at pH = 7.2.

2. Hydrophobic Material Groups ("-focon"):

Group	Description
I	Materials not containing silicon or fluorine
II	Materials containing silicon but not fluorine
III	Materials containing silicon and fluorine
IV	Materials containing fluorine but not silicon

Tables I and II (Manuf/Chem--Appendices A and B) provide a listing of currently-marketed hydrophilic and hydrophobic contact lenses categorized into their appropriate lens grouping and identified by the generic name of the lens material.

III. Claims of Substantial Equivalence:

Applicants who intend to submit 510(k)s generally have three options to demonstrate substantial equivalence to currently marketed lenses from a manufacturing/chemistry perspective (see Flow Chart, Manuf/Chem--APPENDIX C). A side-by-side comparison of physicochemical properties, where applicable, should be provided.

A. Claim of Substantial Equivalence to a Lens with an Existing USAN:

1. The applicant should provide conclusive evidence that the lens material is generically equivalent to a currently marketed lens material through appropriate testing as outlined in this section or by authorization to reference data from the predicate lens. If the lens is found to be generically equivalent to the predicate lens, the lens will be granted the same generic name without the need for approval or confirmation of the USAN Council.

2. If the applicant's lens has the same manufacturing process (e.g., lathe-cut versus lathe-cut) as the marketed lens, or the applicant obtains lens buttons from an approved 510(k) holder or supplier, clinical performance data (see "CLINICAL" section) generally are not required to be submitted in the 510(k). However, any difference in physicochemical properties, especially water content for soft (hydrophilic) contact lens, wetting angle for hydrophobic contact lens, oxygen permeability, modulus, toughness (area under the stress-strain curve), and flexural strength [not applicable to soft (hydrophilic) lens] of the lens should be analyzed statistically and justified in detail to support the claim of generic equivalence.

3. If the applicant's lens has a different manufacturing process (e.g., lathe-cut versus spin-cast) or if the manufacturing process of the predicate lens to which the applicant is claiming substantially equivalent is not known, clinical performance data are generally required to be submitted, along with a side-by-side comparison of physicochemical properties, to establish substantial equivalence, analyzed as in item 2.

B. Claim of Substantial Equivalence to a Lens with the Same Parent USAN but a Different Suffix (Modified Parent USAN):

The applicant who proposes a modification to an existing lens material should demonstrate the following:

1. that the modified lens has an approved parent USAN (the applicant should establish through the USAN Council the new suffix designation for the proposed modification of the parent lens material);

2. that the modified lens falls into one of the lens groups based on the chemical composition, ionic component, and water content of the finished lens;

3. that side-by-side comparison of physicochemical properties of the applicant's lens is compared to a lens containing the same parent USAN;

4. that modulus, toughness, and flexural strength [not applicable to soft (hydrophilic) lens] of the modified lens are in the ranges of approved lenses in that lens group; and

5. that appropriate clinical performance data demonstrate substantial equivalence to the predicate device (see "CLINICAL" section of the guidance).

C. Claim of Substantial Equivalence for a Lens with Different Repeating Monomer Units (New Parent USAN):

The applicant should demonstrate the following:

1. that the lens falls into one of the lens groups in terms of chemical composition, ionic characteristics, and water content;

2. that the applicant has an approved new USAN from the USAN Council;

3. that physicochemical properties of the lens are provided; and

4. that appropriate clinical performance data demonstrate substantial equivalence to the predicate lens (see "CLINICAL" section of the guidance).

IV. Information Needed for Submitting a 510(k) for a Daily Wear Plastic Contact Lens:

CDRH believes that all manufacturing/chemistry data requirements should be met before submitting a 510(k) to FDA. The manufacturer is expected to be in a state of control to produce a consistent product. The Good Manufacturing Practice (GMP) for Medical Devices General Regulation (21 CFR 820) and the Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (21 CFR 58) should be followed by manufacturers in developing their quality assurance programs.

A. The Manufacturer Should Document and Summarize the Following Manufacturing/Chemistry Information:

1. Chemical Composition of the Contact Lens and Purity of Each Monomer Component:

Chemical composition of the contact lens should include monomers, crosslinking agents, initiators, colors (if applicable), UV-absorber (if applicable), and diluents (if applicable) in terms of weight and mole percentage. The actual chemical composition of the finished lens should be calculated by subtracting each initial monomer concentration from residual monomers in the lens blank after polymerization and annealing.

2. Manufacturing Information:

Manufacturing method: (e.g., spin-cast, cast-molded, or lathe-cut)
Polymerization and annealing conditions: time, temperature, and wattage (if applicable)
Manufacturing flow chart and sterilization method (if applicable)

Other manufacturing conditions (e.g., tinting process) (if applicable)
Engineering drawings for lens designs and description
Packaging materials and methods

3. Shelf-life:

In general, the manufacturer should demonstrate the stability of the parameters of the finished lens over time as packaged and stored under the proposed storage conditions. However, the aging of the lens in its container can be extrapolated to the proposed storage temperature.

Assuming first order kinetics, every 10°C increase for the tested temperature above the normal storage temperature will enhance the expiration date by a factor of two. For example, an accelerated stability study at 45°C for 6 months can be expected to be suitable for prediction of a 2-year shelf-life.

A total of 10-20 lenses randomly selected from 2-3 lots are required for shelf-life tests. The stability tests should include physical and optical parameters and the physical appearance of the lens in addition to sterility data (see "MICROBIOLOGY" section). Additional parameters should be monitored for lenses containing color additives, UV-absorbers, or other chemicals during the testing period. Shelf-life extensions should be based on an assessment of the release specifications being within the original established specifications.

Note: For hydrophobic plastic lens materials that are equivalent to currently marketed lenses which do not absorb significant amounts of water (e.g., lenses with <2% water content) and lenses shipped dry, shelf-life studies are not required. However, for hydrophobic plastic lens materials other than conditions mentioned above or any lens materials shipped wet, shelf-life data and proposed shelf-life are required.

4. Compatibility Testing:

The compatibility of the lens with the lens care regimen recommended for use in the proposed lens labeling should be demonstrated by the results of the 30-cycle lens/solution compatibility test. If, however, the recommended lens care products (cleaning/rinsing/disinfection) have been approved for use with lenses of the same lens group for hydrophilic or hydrophobic lenses, the applicant may justify not submitting the compatibility testing in the 510(k) as FDA will consider the compatibility as having been established by the lens care product manufacturer.

5. Leachability:

The leachability of the residual monomers (USP method) and additives (e.g., UV-absorber and tints) should be documented in the 510(k) using the same methodology as for a color additive petition.

6. Finished Lens Parameters:

The physical and optical parameters of the finished lens and their tolerances (e.g., power, base curve, diameter, center thickness, and physical appearances (surface defects, edge defects, bubbles, or granulations)) should be established. FDA recognizes the ANSI Z80.20 standard as an appropriate standard that can be used for establishing tolerances for finished lens parameters.

7. Preservative Uptake/Release:

Such studies will generally be required for new and modified lens materials. However, if the new or modified lens material has no charge or the same electric charge as the preservative system used in the approved care regimen, CDRH will not require preservative uptake/release studies to be submitted in the 510(k). It is important to note, however, that such studies may be useful in establishing substantial equivalence particularly for new and modified lens material (see Manuf/Chem--APPENDIX D for preservative uptake/release test procedures).

8. Physicochemical Properties:

The physicochemical properties of the new lens should be provided and include the following:

a. Color and light transmittance (e.g., UV/Visible Spectrophotometer)
b. Refractive index at ambient temperature [(e.g., 23±2°C) (e.g., measured at 546 nm during the transition period prior to adopting ISO/DIS 9914 with a standard wavelength of 586 nm)]
c. Water content at ambient temperature [(e.g., 23±2°C (e.g., Gravimetric method)
d. In-vitro wetting angle in recommended wetting/soaking/conditioning solution for a period of 7 days (not necessary for hydrophilic contact lenses) (Standard method for determining wetting angle, Contact Lens Manufacturers Association, 421 King Street, Suite 224, Alexandria, VA 22314)
e. Oxygen permeability at 35°C (e.g., ANSI Z80.20 standard or Optometry & Vision Science 67, 476-481, 1990)

f. Mechanical properties at ambient temperature (e.g., 23±2°C): modulus, tensile strength and elongation at break, toughness, and flexural strength [not applicable for soft (hydrophilic) contact lens] [FDA recognizes the ANSI Z80.20 standard or ASTM D1708.84 [for soft (hydrophilic) contact lens] and ASTM D790.92 (for hydrophobic contact lens) as appropriate methods that can be used for measuring mechanical properties of contact lens material].

A side-by-side comparison of the physical/chemical/optical properties of the new lens compared with the lens or lenses to which substantial equivalence is claimed should be provided and analyzed statistically. These include, but are not limited to, water content for soft (hydrophilic) contact lens, wetting angle (for hydrophobic contact lens), oxygen permeability, modulus, toughness and flexural strength [not applicable for soft (hydrophilic) contact lens]. Mean, standard deviation and number of measurements (e.g., a minimum of 30 measurements for not statistically significant differences) should be reported. If the applicant wishes to have a new claim (e.g., reducing protein deposit), supporting information should be described in detail.

9. Suppliers of Lens Blanks:

Evidence should be provided to demonstrate that the lens blanks are safe and effective for their intended use. The lens blank manufacturer should receive 510(k) clearance for the lens blanks. The 510(k) should either contain preclinical data (i.e., manufacturing/chemistry and toxicology) or an authorized reference to an applicable DMF that contains the required information.

a. Soft (hydrophilic) Lens Blanks: A 510(k) is required for lens blanks containing the information noted above. If a manufacturer substitutes his or her supplier of approved lens blanks with another approved supplier of lens blanks made from the same generic material, no new 510(k) is required. However, the manufacturer should document the change in supplier in his or her device history file. If a manufacturer substitutes his or her supplier of approved lens blanks with another approved supplier of lens blanks made from a different generic material, a 510(k) is required for the change.

b. RGP Lens Blanks: If a manufacturer (i.e., finishing laboratory), who is currently manufacturing lenses under the authorization of a lens blank manufacturer, chooses to market a lens with finished lens specifications that differ from those of the lens blank manufacturer (e.g., the applicant's design(s), indications, and labeling are not identical), the finishing laboratory is required to obtain clearance for his or her own 510(k) for the new lens specifications. The finishing laboratory's 510(k)

should include a letter from the lens blank manufacturer indicating that the lens blanks have an approved PMA or SE 510(k). The finishing laboratory would become, by definition, a new manufacturer responsible for all aspects of manufacturing (e.g., conformance to GMPs, compliance with labeling requirements, recordkeeping, registration, listing, etc.).

B. Modifications of an Approved Contact Lens Material Needing a 510(k):

A manufacturer with a substantially equivalent determination for a contact lens may, for a variety of reasons, want to modify the chemical, physical, or optical characteristics of the lens material.

Based on our knowledge and experience with contact lens materials made from plastics, CDRH has been able to characterize certain changes to approved plastic lens materials that could significantly affect safety and effectiveness of the lens and thus require 510(k) clearance. These changes include, but are not necessarily limited to, the following:

1. a change in monomer repeating units including crosslinking agent;

2. a change in ratio of existing monomers which significantly affects physicochemical properties of the lens material;

3. a change in initiators or ratio of initiators which significantly affects physicochemical properties of the lens material;

4. incorporating additives (e.g., color additives or UV-blockers (see Note below));

5. a change in ratio of crosslinking agents which significantly affects physicochemical properties of the lens material;

6. a change in manufacturing processes (e.g., lathe-cut to cast-molded; tinted lens to opaque lens; or a change in the process for adding color additives such as entrapment to reactive); and

7. surface treatment (e.g. reducing protein deposit or improving wettability).

Modifications of a contact lens material may have a significant impact on the performance characteristics of the approved lens. Therefore, the applicant should provide data in the 510(k) sufficient to adequately characterize the modified lens in terms of its physical/chemical/optical, and toxicological performance characteristics when compared to the previously approved lens (see "TOXICOLOGY," "CLINICAL," and "MANUFACTURING/CHEMISTRY" sections).

The results of these studies will determine whether additional clinical performance data will be needed to complete the substantially equivalent determination.

Note: CDRH has developed a procedure which allows a contact lens manufacturer to make lenses with additional colors using listed color additives. This procedure may be implemented at the time of clearance of the initial 510(k) or subsequent to receipt of an SE determination for a colored lens. Specific instructions on how to implement this procedure are listed in the section entitled, "COLOR ADDITIVES AND CONTACT LENSES" (Item II).

MANUF/CHEM--APPENDIX A

TABLE I - LENS GROUPING FOR HYDROPHOBIC PLASTIC CONTACT LENSES

I			II			III	IV
PMMA*	CAB	t-Butylstyrene	Silicone	Silicone Acrylate	t-Butylstyrene/ Silicone Acrylate	Fluoro Silicone Acrylate	Polyperfluoroether
	Meso (cabufocon A)	Airlens (arfocon A)	Silsoft (elastofilcon A)	Paraperm O_2 (pasifocon A)	Opus III (pentasilcon P)	The Boston Equalens (itafluorofocon A)	3M Fluoropolymer (flurofocon A)
	RX-56 (porofocon A)		Sila Rx (dimefocon A)	Oxyflow 39 (pasifocon A)	Saturn II** (synergicon A)	The Boston Equacurve II (itafluorofocon B)	
	Hemlite (porofocon B)		Silcon (silafilcon A)	Paraperm O_2 Plus (pasifocon B)	B & L Synercon** (synergicon A)	Boston RXD (itabisfluorofocon A)	
	Cabcurve (porofocon B)			Paraperm EW (pasifocon C)		Fluoroperm 92 (paflufocon A)	
				Boston II (itafocon A)		Fluoroperm 60 (paflufocon B)	
				Boston IV (itafocon B)		Fluoroperm 30 (paflufocon C)	
				Ocusil (nefocon A)		Fluorex 700 (flusilfocon A)	
				CTL (nefocon A)		Fluorex 500 (flusilfocon B)	
				SGP (telefocon A)		Fluorex 300 (flusilfocon C)	
				B & L RGP (amefocon A)		SGP 3 (unifocon A)	
				Polycon II (silafocon A)		Alberta Lens 'S' (sulfocon A)	
				Polycon HDK (silafocon B)		Menicon SF-P (melafocon A)	
				Optacryl 60 (kolfocon A)		O > Perm F60 (oxyflufocon A)	
				Optacryl K (kolfocon B)			
				Novalens (rosilfocon A)			
				Trans-Aire (amsilfocon A)			
				Bis 56 (amsilfocon A)			

I For materials which do not contain either silicon or fluorine
II For materials which contain silicon but not fluorine
III For materials which contain both silicon and fluorine
IV For materials which contain fluorine but not silicon

* Proposed for class II
** A hydrophilic lens material as a skirt

TABLE II - LENS GROUPING FOR SOFT (HYDROPHILIC) PLASTIC CONTACT LENSES

Group 1

Low Water (<50% H_2O)
Nonionic
Polymers

tefilcon (38%)

- AO Multivue
- Cibasoft
- Cibathin
- Torisoft
- Weicon tinted
- Softint
- Bisoft
- Weicon

tetrafilcon A (43%)

- AO Soft
- AO Soft Super Thin
- Aquaflex Standard
- Aquaflex Super Thin
- Aquaflex Permathin

crofilcon A (39%)

- CSI 38

dimefilcon A (36%)

- Gelflex

polymacon (38%)

- CustomEyes 38
- Vasoft
- PDC
- Softics
- Synsoft
- Cellusoft
- Omega
- Nuview
- SoftView
- Cooper 30
- Hydron
- Hydron Zero
- Hydron Toric
- Hydron Zero T
- Sof-Form II
- Soflens
- Technicon-38
- SecQuence
- Metrosoft II

hefilcon A&B (43%)

- B&L Toric
- Flexlens
- Naturvue
- Miracon
- SoftSite Therapeutic
- SoftSite

phemfilcon A (30%)

- DuraSoft
- DuraSoft TT

isofilcon (36%)

- AL-47

mafilcon A (33%)

- N&N Menicon

Group 2

High Water (≥50% H_2O)
Nonionic*
Polymers

lidofilcon B (79%)

- CW 79
- Sauflon PW

surfilcon A (74%)

- Permaflex

lidofilcon A (70%)

- B&L 70
- Genesis 4
- Sauflon 70
- CV 70
- Hydrosight 70
- Q&E 70
- Lubrisof
- PDC 70
- N&N 70

ofilcon A (74%)

- DuraSoft 4

xylofilcon A (67%)

- Igel

scafilcon A (71%)

- Scanlens

netrafilcon A (65%)

- Signature

atlafilcon A (64%)

- Ciba 2000

Group 3

Low Water (<50% H_2O)
Ionic**
Polymers

etafilcon A (43%)

- Hydromarc
- Vistamarc

bufilcon A (45%)

- Hydrocurve II 45
- Soft Mate

deltafilcon A (43%)

- Armsoft
- Armsoft Thin
- Aquasoft
- Comfort Flex
- Custom Flex
- Metrosoft
- Softact
- Soft Form Toric
- Softics
- Softics Super Plus
- Tripol 43
- Sof-form
- Softflow

droxifilcon A (47%)

- Accugel

phemfilcon A (38%)

- DuraSoft 2
- DuraSoft TT
- DuraSoft 2 Toric

ocufilcon A (44%)

- Tresoft
- Tresoft Thin

Group 4

High Water (≥50% H_2O)
Ionic
Polymers

bufilcon A (55%)

- Hydrocurve II 55
- Hydrocurve II Bifocal

perfilcon A (71%)

- Permalens
- Permalens XL
- Permalens Therapeutic

etafilcon A (58%)

- Vistamarc
- AcuVue

ocufilcon B (53%)

- VT 53

ocufilcon C (55%)

- Ocu-Flex
- O.P.R. -55

ocufilcon D (55%)

- Hydron

ocufilcon E (65%)

- Ocu-Flex 65

phemfilcon A (55%)

- DuraSoft 3
- DuraSoft 3 Toric

tetrafilcon B (58%)

- Aquaflex 58

methafilcon (55%)

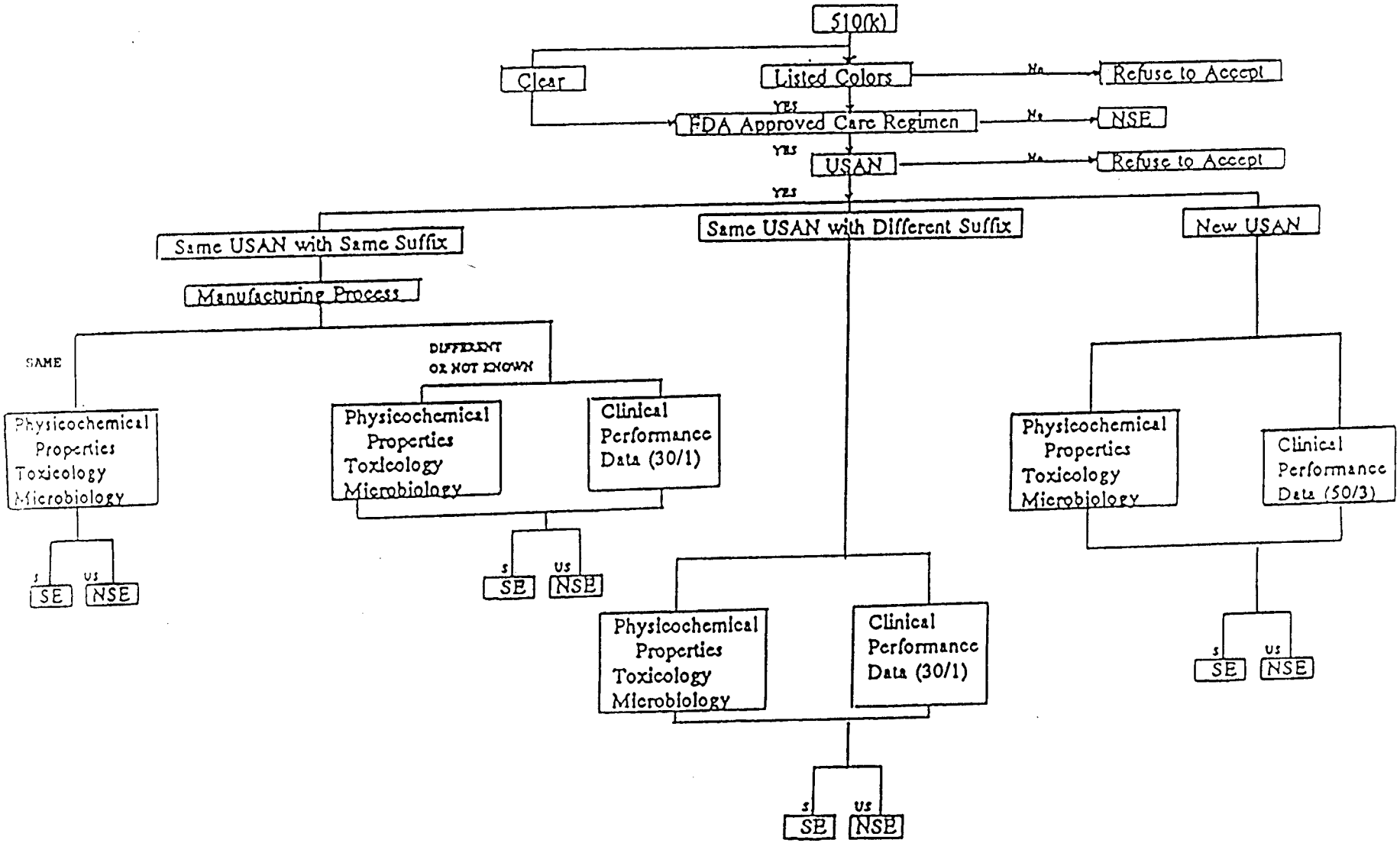
- Hydracon
- Metro 55
- Hydracon Toric

vifilcon A (55%)

- Softcon
- Softcon EW
- NewVues®

* Having an ionic content of ≤1% mole fraction at pH - 7.2
**Having an ionic content of >1% mole fraction at pH - 7.2

FLOW CHART FOR 510(k) DAILY WEAR CONTACT LENS MATERIALS



SE: Substantially Equivalent
NSE: Not Substantially Equivalent

30/1: 30 evaluable subjects followed for 1 month
50/3: 50 evaluable subjects followed for 3 months

MANUF/CHEM--APPENDIX D

PRESERVATIVE UPTAKE/RELEASE TEST PROCEDURES

The test procedures outlined here have been accepted by CDRH for the quantitative analysis of the uptake/release of preservatives, such as thimerosal, chlorhexidine, and benzalkonium chloride, in contact lenses. It is the responsibility of the applicant to select a validated chemical method for the quantitative analysis of the uptake/release of the preservative from the lens, whether it be thimerosal, chlorhexidine, benzalkonium chloride or other newer agents.

In general, a thermodynamically defined "plateau" of total* accumulation of preservative on the lens should be demonstrated for the recommended lens care regimen. Alternatively, the preservative uptake/release studies through equilibration studies can substitute cycling studies (e.g., each lens is soaked in 100 ml care solution at room temperature for 4 days, 8 days, and 12 days or longer).

At least three data points, each separated by at least 20 cycles under the recommended lens care regimen, should be submitted. Each data point should be expressed in terms of the average value, standard deviation, and number of measurements. A statistical analysis should be performed to ensure that it reaches a plateau area. For hydrophilic contact lenses, it should be expressed as μg preservative/mg dry lens; however, for hydrophobic contact lenses, it should be expressed as μg preservative/surface area of lens in cm^2.

A. Thimerosal uptake/release studies of hydrophilic and hydrophobic lens materials by atomic absorption spectrometry:

1. Sample Preparations

   Each lens, after cycling under the recommended care regimen or after a reasonable soaking time in the thimerosal preserved care solution, is placed in a borosilicate vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another borosilicate vial which is used for the preservative uptake study.

2. Preservative Uptake Study

   Five ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated, gently at first on a hot plate until the lens is decomposed. Care should be taken during heating to avoid charring. The vial is then heated strongly to remove all traces of nitric acid, which is determined visually by the presence of white vapor instead of

*Total accumulation of preservative on the lens is a sum of preservative uptake and preservative release data.

**2:1 by volume for hydrophilic plastic lenses.

brown vapor (nitrous oxide) inside the vial. If charring occurs, a few drops of concentrated nitric acid are added and the sample reheated.

The entire sample is employed for the mercury determination using cold vapor atomic absorption spectrometry. Two control lenses, which have been soaked in an isotonic pH = 7.0 buffered saline solution for the duration of the study (35°C for 15 hours), are decomposed and treated as the test lens. Absorbance values for the sample lenses are corrected by subtracting the absorbance value of the control lens.

3. Preservative Release Study

Five ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The solution is treated as the test lens. A control solution (an isotonic pH = 7.0 buffered saline solution) is also treated as the test lens. Absorbance values for the lens leachates are corrected by subtracting the absorbance value of the control solution.

4. Standard Curve

Five ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the vial containing a known concentration of thimerosal standard. The standard solution is treated as the test lens. A reagent blank (concentrated sulfuric: nitric acid = 3.1 by volume) is also treated as the test lens. Absorbance values for the standard solutions are corrected by subtracting the absorbance value of the reagent blank.

B. Chlorhexidine uptake/release studies of hydrophilic and hydrophobic lens materials by ^{14}C-labeled technique:

The procedure for chlorhexidine (CHG) is applicable to any preservative which can be tagged with a non-labile radioactive label.

CHG accumulation by contact lenses is assessed by ^{14}C counting of radiolabeled CHG associated with the lens after the recommended care regimen. The modified procedure of MacKeen and Green*** specifically designed for preservative determination in contact lenses is briefly described as follows:

1. Sample Preparations

Radiolabeled ^{14}C-CHG is added to the care solution containing CHG. Each lens after cycling under the recommended care regimen containing ^{14}C-CHG or after a reasonable soaking time in ^{14}C-CHG

***MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics of Hydrophilic Contact Lenses; J. Pharm. Pharmacol., 30: 578-682, 1978.
MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics in Hard Contact Lenses; J. Pharm. Pharmacol., 31: 714-716, 1979.

preserved care solution is placed in a scintillation vial and bathed in 1 ml isotonic pH ~ 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another scintillation vial which is used for the preservative uptake study.

2. Preservative Uptake Study

Three ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl samples are taken of the resultant solution, mixed with 1 ml of deionized water and 10 ml of Aquasol (New England Nuclear Corporation) with vigorous agitation. After cooling, the samples are counted. The control lens, just removed from the shipping container, is solubilized and treated as the test lens. The counts for the test lenses are corrected by subtracting the counts of the control lens.

3. Preservative Release Study

Three ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl are mixed with 1 ml of deionized water and 10 ml of Aquasol and counted. Duplicate 100 μl of a control solution (an isotonic pH ~ 7.0 buffered saline solution) are also treated in the same way. The counts for lens leachate are corrected by subtracting the counts of the control solution.

4. Standard

Three ml of concentrated sulfuric : nitric acid (3:1 by volume**) are added to the scintillation vial containing 100 μl of ^{14}C-CHG standard solution. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl samples are taken of the resultant solution, mixed with 1 ml deionized water and 10 ml of Aquasol with vigorous agitation. After cooling, the samples are counted.

C. Chlorhexidine Uptake/Release Studies of Hydrophilic Lens Materials by High Pressure Liquid Chromatography (HPLC)

This procedure for chlorhexidine uptake/release studies is applicable to hydrophilic lens materials which show a strong absorption and adsorption to CHG through electrostatic interactions.

The modified procedure of Stevens et al[+] specifically designed for preservative determination in hydrophilic lens materials is briefly described as follow.

Each lens is soaked in 100 ml of care solution at room temperature for 4 days, 8 days, and 12 days or longer. The CHG accumulation by hydrophilic lens materials is assessed by a difference in concentrations of CHG in the care solution before and after lens soaking. After soaking, the lens is removed and placed in 1 ml isotonic pH = 7.0 buffered solution at 35°C for 15 hours (preservative release study). The CHG concentrations in both soaking and elution solutions are determined by injecting sample aliquots of 20 μl directly onto the HPLC column and calculating from the standard.

D. **Benzalkonium chloride (BAK) uptake/release studies of hydrophobic lens materials by laser fluorescence spectroscopy++**

1. Sample Preparation

After cycling under the recommended care regimen or after a reasonable soaking time in BAK preserved care solution, each lens is placed in a vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens that is removed from the vial and air-dried is used for the preservative uptake study.

2. Preservative Uptake Study

Adsorbed BAK is measured by laser fluorescence spectroscopy with an argon laser. The excitation intensity is on the order of 4 x 10^{-6} Einsteins/second, providing a fluorescence spectrum level of 10^3 counts/second at the phototube. For detection, a Hammamatsu photomultiplier tube biased with a Keithley microammeter/high voltage power is used. Monochromators are double JY 0.5 meter holographic gratings.

3. Preservative Release Study

Total adsorbed BAK on the lens is also measured by laser fluorescence spectroscopy. The difference between total adsorbed BAK and adsorbed BAK is the value for preservative release study.

+Stevens, L.E., Durrwachter, J.R., and Helton, D.O.: Analysis of Chlorhexidine Sorption in Soft Contact Lenses by Catalytic Oxidation of ^{14}C-Chlorhexidine and by Liquid Chromatography: J. Pharm. Sci., 75: 83-86, 1986.

++Wong, M.P., Dziabo, A.J., and Kiral, R.M.: Dynamics of BAK Adsorption by Silicone Acrylate Lenses; Contact Lens Spectrum, November. 49-53, 1986.

TOXICOLOGY

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TOXICOLOGY

I. Introduction:

This section of the guidance document discusses the toxicological considerations that CDRH believes should be addressed in order to assess the substantial equivalency (SE), in terms of safety and biocompatibility of the device (i.e., lens blank, finished contact lens and/or plastic container). The manufacturing and chemistry procedures used to fabricate a contact lens as well as the material itself should dictate, in general, the extent of the toxicology testing necessary to establish SE in terms of safety and effectiveness of a lens blank or contact lens. Therefore, the applicant should provide any in vitro or in vivo toxicology or biocompatibility test that will include the necessary data to determine if the device is SE in terms of safety and effectiveness to the predicate device.

It is the applicant's responsibility to develop an appropriate toxicology and biocompatibility profile for the specific lens material. All nonclinical laboratory studies should include a statement that each study was conducted in compliance with the GLP Regulation for Nonclinical Laboratory Studies. If the study was not conducted in compliance with the GLP regulation, a justification of the noncompliance should be submitted.

CDRH is aware of the ongoing research efforts to achieve the goal of eventual substitution of in vitro tests for certain biological tests utilizing animals*. Cell culture methods using corneal epithelial, stromal and endothelial cell lines are currently being researched as in vitro alternatives to in vivo methods. The in vitro Chorioallantoic Membrane (CAM) Assay is based on the fact that the CAM has anatomical components that are similar to the structure of the eye and react to insults with inflammatory responses. However, at present, in vitro alternatives to animal testing have not been sufficiently developed or validated for use. Therefore, CDRH regrets that toxicology tests involving animals will continue to be used at this time in order to adequately assess risks and evaluate safety of ocular products prior to 510(k) clearance. CDRH will continue to monitor the developments of alternatives to animal testing and will recommend their use once such studies have been validated.

The toxicology studies recommended below are generally consistent with the applicable studies recommended for evaluating plastic polymers in the Tripartite Biocompatibility Guidance for Medical Devices, which categorizes contact lenses as Externally Communicating Devices: Intact Natural Channels. The Tripartite Guidance has been harmonized with the International Standards Series ISO 10993, Biological Evaluation of Medical Devices.

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*Goldberg, A.M., et al. Framework for Validation and Implementation of In Vitro Toxicity Test: Report of the Validation and Technology Transfer Committee of the Johns Hopkins Center for Alternatives to Animal Testing. J. Am. Coll. Tox. 1993: 12:23-30.

NOTE: In addition to the recommended tests listed, CDRH believes that the material safety data sheet (MSDS) should be submitted for each chemical constituent incorporated into the finished lens. CDRH is aware that additional safety and toxicology data are generally included on the MSDS which can be obtained from the supplier of the chemical constituent. When scientifically appropriate, information from the MSDS may be used to support safety and biocompatibility of a new chemical constituent (e.g., UV-absorber) in lieu of performing additional or repetitive toxicology testing. The MSDS should be included in the 510(k) submission.

II. Minimum Recommended Toxicology Test Procedures for Class II Contact Lenses:

A. Systemic Injection Test (USP)**:

The purpose of this study is to assess the potential of leachable chemical constituents from a contact lens material to produce an acute systemic toxicity in mice. Extracts of the lens material are prepared in two types of solvents (polar and non-polar), injected into mice, and the mice observed for acute systemic toxicity.

B. Eye Irritation Test (USP)**:

The purpose of this study is to evaluate the potential for ocular irritation resulting from residual chemical leachables in contact lens materials. The effects are assessed *in vivo* using rabbits.

C. Cytotoxicity Test (USP)**:

The purpose of this study is to evaluate the potential for cytotoxicity resulting from residual chemical leachables in contact with lens materials. The effects are assessed *in vitro* using cytotoxicity studies; (e.g., tissues culture-agar overlay method or a suitable validated alternative).

**United States Pharmacopeia XXI/National Formulary XVI (or current update) --Containers for Ophthalmics--Plastics (Biological Test Procedures).

III. Additional Recommended Testing:

The following three tests (i.e., Preservative Uptake and Release, Guinea Pig Maximization Test and Three Week Ocular Irritation Test in Rabbits) will not be required to be submitted if the applicant provides appropriate documentation demonstrating that either of the following criteria have been met:

- the recommended lens care regimen has been approved for use with the specific lens material group; or

- the plastic lens carries no charge or the same electric charge as the preservative system used in the approved care regimen.

However, these tests will be required if:

- a lens material is manufactured using a new monomer not previously used in a currently marketed hydrophilic or hydrophobic lens; or

- a UV-absorber is incorporated into the material unless a scientific justification is provided to the contrary (e.g., use of a UV-absorber that has been previously cleared by the manufacturer for use in contact lenses of the same generic class (i.e., hydrophilic or hydrophobic materials) and will be incorporated into the lens by a method that has been approved in a PMA or cleared in an SE 510(k) for the manufacturer.

A. Sensitization Tests:

1. Preservative Uptake and Release:

Contact lens polymers may absorb or adsorb preservative materials that could possess irritating or sensitizing properties that are potentially irritating to some users. If the lens does not meet either of the criteria noted below, manufacturers should provide CDRH with the amount of preservative uptake per lens and the amount released under a worst case scenario (e.g., a thermodynamically defined plateau of total accumulation of preservative on the lens). (See Manuf/Chem--Appendix D for suggested test procedure for this test.)

2. Guinea Pig Maximization Test:

The purpose of the test is to grade or rank chemical constituents on a scale of I through V as to their potential for inducing sensitivity response in the guinea pig model. The grades of rankings are based on the number of animals sensitized, and the results are classified on an ascending scale from a weak sensitizing agent (grade I) to an extreme sensitizing agent (grade V).

Magnusson, B. and Kligman, A.M. The Identification of Contact Allergens by Animal Assay. The Guinea Pig Maximization Test. J. Invest. Dermatol. 1969; 52.

B. Three Week Ocular Irritation Test in Rabbits:

The purpose of this in vivo test of the contact lenses in rabbits can be used as a biocompatibility test as well as a toxicity test of the lens material to assess the in vivo effects of the lens material on the ocular tissues (see next page for an example of test design).

IV. The Required Toxicology Tests for Plastic Containers are as Follows:

The purpose of these testing requirements is to indirectly or directly access the potential toxicity of any constituent(s) that may leach from the container when the packaging solution comes in contact with the contact lens(es) for a prolonged period of time. The following in vitro and in vivo test procedures are recommended by CDRH and are consistent with the procedures listed in USP/National Formulary under the section, Containers for Ophthalmics--Plastics (Biological Test Procedures).

A. Systemic Injection Test (USP)

B. Eye Irritation Test (USP)

C. Cytotoxicity Test (USP)

V. Three Week Ocular Irritation Test in Rabbits:

The following presents an EXAMPLE of a test design that can be used as a general guidance in developing an appropriate in vivo ocular irritation test of a contact lens made of a plastic material. It is the responsibility of the applicant to design an appropriate in vivo test using a sufficient number of animals to assess the safety and biocompatibility when using the recommended lens care regimen.

CDRH suggests that this in vivo ocular irritation test be performed in the rabbit model. Test lenses for the test should be lenses of the greatest mass as they are to be sold. Appropriate controls (e.g., eyes receiving no lens or eyes receiving a control lens) should be included in the test design. A minimum of 12 rabbits, determined to be free of corneal defects by initial slit lamp examination with fluorescein staining, should be randomly distributed into groups similar to the proposed groupings outline in the example below:

Total of 12 Rabbits - 6 male/6 female (24 total eyes)

Group 1 (males)	-	3 normal eyes fitted with the test lenses that have been treated with disinfection procedures proposed for patient use.
Group 2 (females)	-	3 normal eyes fitted with the test lenses that have been treated with disinfection procedures proposed for patient use.
Group 3 (males)	-	3 normal eyes fitted with the test lenses that have not been treated with disinfection procedures proposed for patient use.
Group 4 (females)	-	3 normal eyes fitted with the test lenses that have not been treated with disinfection procedures proposed for patient use.

The following procedures should be included in the study protocol:

A. Adult albino rabbits (6-10 lbs.) generally healthy and with clinically normal eyes should be used. The status of the eyes should be judged by gross, slit lamp and/or another appropriate means.

B. Excision of the nictitating membranes is optional. If excision is made, a minimum of 2 weeks should pass before beginning the experiment. The test lenses are inserted each morning and removed in the evening for a wearing period of at least 8 hours per day. If a lens is rejected, it is cleaned and then reinserted. After the lenses are worn each day, they are removed and disinfected (where applicable) according to the instructions of the manufacturer.

C. A contact lens should be fitted to the cornea of the right eye of each animal, and the left eye should be used for control purposes as dictated by the test protocol. The lenses should be allowed to remain in place for at least 8 hours each day for 21 days.

D. After the initial fitting of the lenses, the adequacy of the fit on the animal eyes should be checked by means of fluorescein or other appropriate methods.

E. Eyes should be examined daily and the status scored by use of a slit lamp using the Hackett-McDonald method* or a suitable alternative scoring method. If the Hackett-McDonald scoring method is not used, both eyes of all animals should be examined weekly with the aid of a slit lamp and fluorescein staining. Separate records should be maintained for each animal.

F. The assessment of corneal metabolism and/or viability of a representative sampling of corneas should be determined. The use of Rose Bengal may be used to ascertain viability or an appropriate alternative method may be used. The corneal metabolism study need not be performed when a manufacturer makes a polymer modification to an approved lens if the manufacturer can demonstrate the oxygen permeability (Dk) of the modified lens is increased or remains the same as that of the approved lens.

G. All lenses used in the test should be retrieved at the termination of the experimental period for purposes of assessing the in vivo effects of the ocular environment on the lens material when using the recommended lens care regimen. The information submitted in a 510(k) should include, but not be limited to, data that compare the physical and optical parameters of the lens, such as physical appearance (e.g., lens discoloration, protein deposits, chipped or pitted lenses, center thickness and lens powers as measured before starting test and after termination of the test).

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* F.N. Marzulli and H.L. Maibach, eds., Dermato. Toxicology 4th Ed, Hemisphere Pub. Corp., pages 749-815, 1991.

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