This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer 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 will be updated in the next revision to include the standard elements of GGP's.

DEPARTMENT OF HEALTH & HUMAN SERVICES | Public Health Service

Memorandum

Date JUN 28 1994

From Associate Director for Contact Lens Devices (HFZ-460)

Subject Amendment 1 to May 12, 1994, PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES

To Contact Lens Manufacturers and Other Interested Persons

Pages 18 and 20 of the May 12, 1994 PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES have been revised to make a mathematical correction in Section IV.A.1 (page 18) and to improve sentence structure in item 5 (page 20). Please replace these pages with the attached corrected pages.

David M. Whipple

Attachments

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 residual monomers from each initial monomer 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) (using the same methodology as for a color additive petition) should be documented in the 510(k).

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)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

July 27, 1994

Dear Contact Lens Premarket Approval Application (PMA) Holders:

On March 10, 1994, the Center for Devices and Radiological Health (CDRH) provided all premarket approval application (PMA) holders with copies of the November 1993 PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES. The purpose of this letter is to notify all PMA holders that the MAY 12, 1994 DOCUMENT (COPY ENCLOSED) REPLACES THE NOVEMBER 1993 VERSION AS THE APPROPRIATE GUIDANCE DOCUMENT THAT CONTAINS THE "SPECIAL CONTROLS" AND SHOULD BE FOLLOWED FOR SUBMISSIONS OF ALL 510(k)s. PLEASE READ THIS DOCUMENT CAREFULLY BECAUSE IT CONTAINS IMPORTANT ADDITIONS, DELETIONS, AND REVISIONS FROM THE NOVEMBER 1993 VERSION.

CDRH calls your attention to specific recommendation in the May 12, 1994 revision of the guidance that were not in the November version, such as the following:

1. Adding the cautionary labeling statement to rigid gas permeable (RGP) contact lens labeling: "Caution. Non-sterile. Clean and condition lenses prior to use." CDRH expects this labeling change to be implemented within 6 months of the date of this letter, or at the next printing of labeling, whichever is sooner. Although this guidance document pertains to daily wear lenses, CDRH believes that the cautionary statement should also be included on labeling for class III extended wear RGP lenses.

2. Making corrections as recommended on page 52 (item e) of the guidance to the labeling for presbyopic patients.

We are also enclosing a copy of amendment 1 which contains revisions explained in the cover letter dated June 28, 1994. Additional amendments that contains revisions that are made at future dates will be provided to the Division of Small Manufacturers Assistance (DSMA) for distribution (see address and telephone number in attached guidance cover letter). You should check with DSMA periodically to determine if additional amendments are available.

CDRH reminds you that if you have an approved PMA for a daily wear plastic lens only, you are no longer subject to PMA annual reporting requirements. Therefore, if you have not notified FDA that your PMA is for daily wear lenses only, you should immediately report this information to us, at the following address, so that we can adjust our records accordingly.

Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

If you have questions about the contents of the enclosed guidance, please contact James F. Saviola, O.D. at (301) 594-1744 or David M. Whipple at (301) 594-2205.

Sincerely yours,

for Nancy C. Brogdon
Interim Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

May 12, 1994

Dear Contact Lens Manufacturers or Interested Persons:

The enclosed PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES contains the special controls which have been determined by the Center for Devices and Radiological Health (CDRH) to be necessary to provide reasonable assurance of the safety and effectiveness of class II contact lenses in the absence of an applicable standard.

This guidance was initially provided to the public on November 18, 1993, at which time the agency requested comments from interested persons. As discussed at the March 22, 1994, meeting of the Ophthalmic Devices Panel (Panel), FDA has evaluated the comments received and is revising the guidance document incorporating changes and those comments determined to have scientific merit.

PLEASE NOTE THAT THE MAY 12, 1994, DOCUMENT REPLACES THE NOVEMBER 1993 VERSION AS THE APPROPRIATE GUIDANCE DOCUMENT THAT CONTAINS THE "SPECIAL CONTROLS" AND SHOULD BE FOLLOWED FOR SUBMISSION OF A 510(k). PLEASE READ THIS DOCUMENT CAREFULLY BECAUSE IT CONTAINS IMPORTANT ADDITIONS, DELETIONS, AND REVISIONS FROM THE NOVEMBER 1993 VERSION.

The Safe Medical Devices Act (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional daily wear soft or daily wear nonhydrophilic plastic contact lenses in class II if, within 36 months of enactment, FDA has not determined that the lenses must remain in class III. SMDA also requires that appropriate regulatory safeguards (i.e., special controls) be in effect when reclassification occurs. An order effective March 4, 1994, published in the FEDERAL REGISTER (59 FR 10397 March 4, 1994) announced the reclassification of daily wear soft and daily wear nonhydrophilic plastic contact lenses. FDA identifies the reclassified generic types of devices as follows:

1. Rigid Gas Permeable Contact Lens: A daily wear rigid gas permeable (nonhydrophilic) contact lens is a device intended to be worn directly against the cornea of the eye to correct vision conditions. The device is made of various materials, such as cellulose acetate butyrate, polyacrylate-silicone, or silicone elastomers whose main polymer molecules generally do not absorb or attract water.

2. Soft (hydrophilic) Contact Lens: A daily wear soft (hydrophilic) contact lens is a device intended to be worn directly against the cornea and adjacent limbal and scleral areas of the eye to correct vision conditions or act as a therapeutic bandage. The device is made of various polymer materials, the main polymer molecules of which absorb or attract a certain volume (percentage) of water.

The reclassification order does not apply to contact lenses intended for extended wear nor to contact lens accessories, all of which remain in class III. FDA intends to review the classification of contact lens

accessories and may propose reclassification in the future. Also, this order does not apply to polymethylmethacrylate (PMMA) contact lenses which have not yet been classified. FDA intends to move toward final classification of PMMA lenses in the near future.

This document should be used as guidance for all submissions made after reissuance on May 12, 1994. Manufacturers should be aware that although this document represents the special controls required by SMDA, it is considered a living document and is expected to be impacted by ongoing policy initiatives within CDRH and FDA's efforts to harmonize its data requirements with international standards. Any significant updates or changes in data requirements will be announced at forthcoming meetings of the Panel. Although comments received to date have been considered prior to this revision, interested persons may submit written comments at any time, which will be incorporated in future updates of this guidance if CDRH determines that they are appropriate. Comments should be submitted to:

Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Interested persons may obtain copies of the May 12, 1994, guidance document by contacting:

Division of Small Manufacturers Assistance (HFZ-220)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Telephone: (800) 638-2041
(301) 443-6597

I would like to take this opportunity to thank the Panel members, contact lens industry and other interested persons for taking the time and effort to evaluate and comment on this special controls document. In addition, I would like to thank the members of the Contact Lens Branches and others who have worked extremely hard in preparing this guidance document.

Sincerely yours,

for Nancy C. Brogdon
Interim Director
Division of Ophthalmic Devices
Office of Devices Evaluation
Center for Devices and
Radiological Health

Enclosure

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES

REVISED MAY 1994

Prepared by:

Contact Lens Branch
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR
DAILY WEAR CONTACT LENSES

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INTRODUCTION

The Safe Medical Devices Act of 1990 (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional daily wear soft or daily wear nonhydrophilic plastic contact lenses in class II, if within 36 months of enactment, FDA has not determined that the lenses must remain in class III. FDA issued an order announcing the reclassification of daily wear soft and daily wear nonhydrophilic plastic contact lenses (defined in 21 CFR 886.5916 and 886.5925) from class III (premarket approval) into class II (special controls), effective March 4, 1994 (59 FR 10397). SMDA also requires that appropriate regulatory safeguards (i.e., special controls) be in effect at the time of reclassification which provide reasonable assurance of the safety and effectiveness of such lenses, including clinical and preclinical data, if necessary. This guidance document sets forth the special controls needed to assure the safety and effectiveness of daily wear plastic contact lenses and the evidence needed to demonstrate the substantial equivalence of new lenses to lenses already marketed. For purpose of this guidance document, the term "class II" is used to describe a generic type of contact lens intended for daily wear only. However, each manufacturer should be aware that an unapproved individual contact lens is not a class II device until it has been determined to be a class II device by clearance through the premarket notification (510(k)) process.

Definition of Contact Lenses Covered by this Guidance Document:

Class II contact lenses are defined in 21 CFR 886.5916 and 886.5925, and generally include daily wear soft (hydrophilic) and hydrophobic (nonhydrophilic, such as rigid gas permeable [RGP]) contact lenses which have the following intended uses: (1) non-therapeutic contact lenses (e.g., refractive ametropia [myopia, hyperopia and astigmatism], aphakia, and presbyopia [bifocal and multifocal]), (2) specialized use contact lenses (e.g., keratoconus), and (3) therapeutic daily wear contact lenses. Contact lenses remaining in class III would include those intended for extended wear. Manufacturers intending to market a class III contact lens should consult the booklet, "April 1989 Guidance Document for Class III Contact Lenses" (April 1989 Guidance) available from the Division of Small Manufacturers Assistance (DSMA) at (1-800) 638-2041 or (301) 443-6597 or the Division of Ophthalmic Devices (DOD) at (301) 594-1744.

Contact lens manufacturers should be advised that reclassification of daily wear plastic contact lenses from class III to class II impacts the April 1989 Guidance. All references in the April 1989 Guidance to daily wear lenses are no longer applicable and are superseded by the "PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES (Revised May 1994)." The April 1989 Guidance may continue to be used as a guidance for administrative policies and procedures and as guidance for some preclinical testing for extended wear contact lenses. However, manufacturers should be aware that the "PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES (Revised May 1994)" results in changes in some preclinical requirements for contact lenses (e.g., changes in microbiology requirements for hydrophobic contact lenses and modifications in lens groupings in the manufacturing/chemistry section). In addition, as FDA re-evaluates its data requirements for extended wear contact lenses and works to harmonize its

requirements with international standards, significant changes in our guidance may be forthcoming. Such changes may include modifications in test methods, definitions, and especially in the design of clinical trials for extended wear lenses, all of which are now being considered. Any changes in requirements will be announced at forthcoming meetings of the Ophthalmic Devices Panel. Meanwhile, manufacturers proposing to conduct studies of extended wear contact lenses are encouraged to contact DOD if they have questions about preclinical testing requirements (e.g., microbiology, manufacturing/chemistry) and to discuss their protocol(s) prior to submitting investigational device exemption (IDE) applications for extended wear studies.

This guidance document does not address the testing requirements for lenses made entirely of polymethylmethacrylate (PMMA) which are currently unclassified. PMMA lenses were proposed for classification as class II but did not receive final classification when the final classification regulation for ophthalmic devices was published (Ophthalmic Devices; General Provisions and Classifications of 109 Devices, Federal Register, September 2, 1987 [52 FR 33346]). Final classification was withheld until PMMA could be identified. The Center for Devices and Radiological Health (CDRH) is planning to issue a Federal Register notice for comment on the regulation of PMMA lenses; however, such a notice has not been published as of the date of this guidance document. Meanwhile, manufacturers proposing to market PMMA lenses are required to submit a 510(k) according to section 510(k) of the Food, Drug and Cosmetic Act (the act). For guidance on submitting a 510(k) for a PMMA lens, manufacturers should contact DSMA or DOD (telephone numbers above).

Purpose of Document:

This document is intended to provide comprehensive directions to enable a manufacturer of a daily wear plastic contact lens to submit a 510(k) that will adequately demonstrate whether the lens is substantially equivalent to a legally marketed daily wear plastic contact lens (predicate device). Guidance is provided on the preclinical and clinical tests which should be used to demonstrate substantial equivalence. If clinical performance data are needed, this guidance provides directions for obtaining an IDE.

To obtain an IDE, an adequate investigational plan and informed consent document must be presented to an institutional review board (IRB) for review and approval. IRB approval is always required before initiating a clinical study of both significant risk and non-significant risk devices. FDA considers clinical studies of daily wear soft or daily wear nonhydrophilic plastic contact lenses to be nonsignificant risk investigations. FDA considers clinical studies of extended wear contact lenses or daily wear lenses made of non-plastic materials to be significant risk investigations and require both IRB and FDA approvals before initiating clinical testing. The clinical performance data collection must be conducted in accordance with an investigational plan that will ensure subject protection and the development of data adequate to demonstrate the substantial equivalence of the lens to a legally marketed lens.

The preclinical portion of this document consists of manufacturing/chemistry, toxicology, and microbiology sections outlining the types of manufacturing data and preclinical testing that should be completed prior to submitting a 510(k) or, if clinical performance data are necessary to demonstrate substantial equivalence, prior to seeking IDE approval from an IRB. Each section includes a summary of the basic requirements and suggested methods for meeting these requirements.

The clinical portion of this document includes the major elements of clinical performance data collection and suggested methodologies to be included in the protocol. The clinical protocol is part of the investigational plan that must be submitted to an IRB in order to obtain approval of an IDE.

Other elements of the guidance document include: (1) general information on the applicable regulations and requirements for labeling of contact lenses, (2) requirements for modifications of a legally marketed contact lens ("MANUFACTURING/CHEMISTRY," "TOXICOLOGY," and "CLINICAL" sections), and (3) additional guidance including suggested methodologies for meeting color additive requirements (e.g., meeting listing requirements in order to comply with section 721 (section 706 prior to July 1993 revision) of the act and procedure for incorporating "listed" color additives in contact lenses); procedure for adding lens finishing laboratories for manufacturing and marketing of daily wear plastic RGP contact lenses; and procedure for implementing changes in packaging materials.

The information in this guidance document is intended to assist persons in the collection and preparation of data for a 510(k) submission. This guidance does not bind the agency, and it does not create or confer any rights, privileges, or benefits on or for any person. This document does not create legal requirements, but does set forth the preclinical and clinical testing that FDA believes are acceptable to establish substantial equivalence as required by the act.

While use of this document to prepare preclinical and clinical protocols will not ensure IDE approval or 510(k) clearance, following the recommendations of this document should ensure that the necessary tests are conducted. A substantial equivalence determination for a 510(k) can be expected to follow if tests are conducted properly, data are adequately analyzed and presented, applications are submitted in accordance with applicable regulations, and the test results show that the lens is substantially equivalent to a legally marketed daily wear plastic lens.

Persons may choose to follow the guidance herein or may follow different data collection and preparation procedures and protocols. If a person chooses to follow different collection and preparation procedures and protocols, a person may discuss the matter in advance with CDRH to prevent the expenditure of money and effort on an activity that may later be determined to be unacceptable.

If alternate procedures are used, the applicant should be prepared to demonstrate to CDRH's satisfaction that such procedures demonstrate the substantial equivalence in terms of safety and effectiveness to the predicate device.

Preclinical or clinical data in other documents on file with CDRH may be incorporated by reference into a 510(k). To be referenced, documents such as IDEs, 510(k)s, premarket approval applications (PMAs) or device master files (DMFs) should have been submitted by the applicant, or the applicant should provide CDRH with appropriate authorization from the submitter. This authorization should be in the form of a letter addressed to the Document Mail Center, HFZ-401, CDRH, 1390 Piccard Drive, Rockville, Maryland 20850, referencing the correct document number.

DOD should be consulted if questions remain after reading this document. DOD's telephone number is provided above.

Pertinent Regulations:

The FDA regulations especially relevant to class II contact lenses are:

- Device Classes (section 513(a)(1) of the act)
- Establishment Registration and Device Listing for Manufacturers of Devices (21 CFR 807)
- Premarket Notification Procedures (21 CFR 807, Subpart E)
- Investigational Device Exemptions (21 CFR 812)
- Protection of Human Subjects; Informed Consent (21 CFR 50)
- Institutional Review Boards (21 CFR 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR 58)
- Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7)
- Good Manufacturing Practice for Medical Devices: General (21 CFR 820)
- Medical Device Reporting (21 CFR 803)
- Listing and Certification of Color Additives for Foods, Drugs, and Cosmetics (section 721 of the act and 21 CFR, Parts 70 through 74)
- Labeling (21 CFR 801)

Each of these regulations is briefly discussed below.

Device Classes (Section 513(a)(1) of the Act):

Class II devices are subject to both general and special controls. General controls include the prohibition on adulteration (section 501 of the act); prohibitions on misbranding (section 502 of the act); banned devices (section 516 of the act); notification of risks and repair, replacement, or refund (section 518 of the act); records and reports (section 519 of the act); restricted devices (section 520(e) of the act), Good Manufacturing Practices (section 520(f) of the act); registration of establishments (section 510 of the act); listing of devices (section 510(j) of the act); and submission of a premarket notification (section 510(k) of the act). Special controls may include the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in 510(k) submissions in accordance with section 510(k)), recommendations, and other appropriate actions as deemed necessary to provide reasonable assurance of the safety and effectiveness of the device.

Establishment Registration and Listing for Manufacturers of Devices (21 CFR 807):

Medical device manufacturers, initial distributors (U.S. importers), and distributors are required to register their establishments by supplying CDRH with the information required on registration form FDA 2891 (Initial Registration of Device Establishments). Manufacturers are also required to list their devices in commercial distribution in the U.S. by completing form FDA 2892 (Medical Device Listing). Foreign manufacturers may, but are not required to register; however, they must list their devices. Questions about registration and listing may be addressed to DSMA (telephone number above).

Premarket Notification Procedures (21 CFR 807, Subpart E):

Most devices are cleared for commercial distribution or marketing in the U.S. through the 510(k) process. In this process, the manufacturer makes a 510(k) submission to CDRH and must receive a letter or order from CDRH permitting commercial distribution. This order is based on CDRH's finding the device substantially equivalent to a device legally marketed in the U.S. The manufacturer or importer must provide in the submission, among other things, evidence of such substantial equivalence. What constitutes substantial equivalence is explained in section 513(i)(1)(A) of the act. Substantial equivalence means that a device has the same intended use and the same technological characteristics (i.e., design, material, function, and other similar features) as the predicate device; or has the same intended use and new technological characteristics, but it can be demonstrated that the device is as safe and effective as the predicate device and does not raise different types of questions regarding safety and effectiveness from the predicate device.

The 510(k) notification requirement applies: whenever a manufacturer markets a device for the first time; when there is a change in the intended use; or whenever an existing device being marketed is modified in a way that could significantly affect its safety and effectiveness. It is not intended that a 510(k) be submitted for every insignificant change, but only where such changes could significantly affect safety or effectiveness. CDRH believes that the manufacturer is best qualified to make the initial determination, which should be based on the exercise of good judgment, adequate supporting data, and sufficient documentation. The manufacturer should be aware, however, that if he or she makes a decision not to submit a new 510(k), CDRH can overrule that decision and take appropriate regulatory action. If a manufacturer does make a change or modification to the device and does not submit a 510(k), he or she should document the reason for not submitting a 510(k) in the good manufacturing practice (GMP) device master record and make it available to FDA upon request.

Section 807.81 Subpart E of 21 CFR (Premarket Notification Procedures) provides guidance on the type of changes for which an applicant must submit a 510(k) if the change could significantly affect the safety and effectiveness of the device. Additionally, you should contact DSMA (telephone number above) to obtain a copy of the most recent CDRH general guidance on changes to an existing device that would require submission of a new 510(k). Manufacturers should be aware, however, that a device specific guidance document such as the "PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES" supersedes a CDRH general guidance involving device modifications requiring submission of a new 510(k). If, after attempting to evaluate the change, manufacturers are still uncertain about the need for a 510(k), they may write a letter explaining the changes in detail, referencing the 510(k) number, and mail it to the Document Mail Center, CDRH.

Once a 510(k) has been submitted, additional information may be requested by CDRH, in which case the 510(k) application will be placed on hold. A letter is issued stating that the file will be retained for 30 days while waiting for the submitter's response. If a response is not received within 30 days, the 510(k) may be deleted. The submitter should respond within 30 days or, if the 30-day period cannot be met, request an extension by letter to the Document Mail Center, CDRH (address above), referencing the 510(k) number. When CDRH receives the additional information, the review period begins again. This happens each time additional information is requested.

Premarket notification review allows CDRH to find not substantially equivalent (NSE) devices that: (a) present new types of questions of safety and/or effectiveness relative to the predicate devices; (b) appear to be less safe or effective than legally marketed devices; and (c) have indications that are a new intended use.

If CDRH determines that a device is NSE, the manufacturer may appeal the NSE decision, file a reclassification petition, or submit a PMA. When a manufacturer and CDRH disagree about the NSE decision for a device, the following applies:

- A device that CDRH finds to be NSE is automatically classified into class III, and unless reclassified into class I or II, is subject to premarket approval. The manufacturer may request reconsideration of an NSE decision. The 510(k) Staff may be contacted at (301) 594-1190 for information on how to request reconsideration of an NSE decision.

- Under section 513(f) of the act, a manufacturer of a class III device may petition CDRH for reclassification of this device into class I or class II. CDRH will refer a petition to the appropriate FDA advisory panel for review and recommendation. The content and format requirements of a reclassification petition are in 21 CFR 860.123.

- The manufacturer may resubmit another 510(k) with new data.

A 510(k), including information described in Subpart E of 21 CFR 807, should be submitted in duplicate on standard sized paper with pages numbered, securely bound (if necessary), and three-hole punched. The manufacturer should designate in the cover letter that the submission is a "510(k) notification." All attachments to the 510(k) submission should be appropriately identified.

Under SMDA, the 510(k) submitter must include either a summary of the safety and effectiveness information upon which the substantial equivalence determination is based, or a statement in the 510(k) that the submitter will make available the safety and effectiveness information to interested persons upon request. If a statement is provided, it should state the following:

> "I certify that [name of person required to submit the premarket notification] will make available all information included in this premarket notification on safety and effectiveness that supports a finding of substantial equivalence within 30 days of request by any person. The information I agree to make available does not include confidential patient identifiers."

The booklet "Premarket Notification 510(k): Regulatory Requirements for Medical Devices" (HHS Publication FDA 92-4158) provides detailed explanations and examples of ways that companies can comply with the 510(k) requirements. DSMA can provide you with this booklet, answer questions, and provide guidance regarding the regulatory process. DSMA's telephone numbers are listed above.

Investigational Device Exemptions (21 CFR 812):

Data from clinical testing may be necessary to demonstrate the substantial equivalence of a daily wear plastic contact lens to a legally marketed lens. To collect these clinical data, an approved IDE is required before the sponsor (usually the manufacturer) can distribute investigational medical devices for clinical testing. The IDE regulation describes procedures for obtaining an approved IDE and outlines the responsibilities of a sponsor and an investigator during a clinical investigation with a medical device.

FDA considers clinical studies of daily wear soft or daily wear nonhydrophilic plastic contact lenses to be non-significant risk investigations. Therefore, the abbreviated requirements of the IDE regulation apply [21 CFR 812.2(b)] which basically require the following:

1. The sponsor must submit and obtain approval for a non-significant risk device study from a properly constituted IRB (21 CFR 56), or FDA if no IRB exists (21 CFR 812.62(b)), prior to distributing devices for a clinical investigation (21 CFR 812.30).

2. All test subjects must give their informed consent (21 CFR 50) before being treated with the investigational device. Informed consent is obtained on a written form advising the subjects of their rights as voluntary research subjects, apprising subjects of risks, benefits, and alternate procedures, if any, and test procedures involved.

3. All investigations must be properly monitored.

4. Recordkeeping and reporting requirements must be met.

FDA review and approval is not required for an investigation of a non-significant risk device. A sponsor needs to obtain IRB approval and follow the requirements of 21 CFR 812.2(b)(1)(i) through (vii). Class III contact lenses are considered significant risk devices and require both IRB and FDA review and approval.

Although FDA does not normally consider daily wear contact lens clinical studies to be significant risk investigations, the determination that a particular contact lens or other product poses a non-significant risk to a subject is concurred by the IRB. For a device investigation to be determined to be non-significant risk, a sponsor must provide an IRB with a statement of why the investigation does not pose a significant risk, and the IRB must agree with this assessment. The IRB must also approve the investigation as a non-significant risk study. IRBs must be provided with all information necessary to reach a sound decision. This information, in the case of contact lenses, must include informed consent forms and the clinical protocol. It is important to note that, in the case of non-significant risk investigations, although preclinical data are not required to be submitted to CDRH until a 510(k) is submitted, these tests must be conducted and evaluated prior to initiating a clinical study. The purpose of preclinical tests is to evaluate whether subjects will be at undue risk, and thus preclinical test results should be submitted to the IRB for its review prior to testing in humans.

IDE Study Design:

Sponsors of investigations should consider carefully how to adequately demonstrate the substantial equivalence of their specific devices to legally marketed devices and design their study to assure that the data provide valid scientific evidence, as defined in 21 CFR 860.7; to answer all clinical objectives properly; and to form a sound basis to support the intended use and claim(s) being made in the labeling.

Manufacturers should carefully review the "CLINICAL" section of this guidance document, which has been designed to assist in developing an adequate clinical protocol. In addition, they should consult with the DOD scientific staff, if necessary, when preparing their clinical protocol. The preparation of an adequate protocol is one of the most important aspects of the clinical investigation and essential for a successful 510(k) when clinical performance data are required to demonstrate substantial equivalence. The protocol should be designed to fully support the proposed labeling claim(s) and intended use of the device. The sponsor is responsible for ensuring that the study design is appropriate and that all necessary tests are completed. If alternative tests are more appropriate than those listed or additional tests must be conducted, the overall design of the study and its justification are the responsibility of the study sponsor.

Information available to sponsors includes the IDE regulation (21 CFR 812) and related information. Please contact the IDE Staff at (301) 594-1190 or DOD (telephone number above) for further guidance.

Protection of Human Subjects; Informed Consent (21 CFR 50):

The fundamental purposes of IRB review and of informed consent are to assure that the rights, safety, and welfare of subjects are protected. A signed informed consent form is evidence that the information required by section 50.25 has been provided to a prospective investigational subject. IRB review of the form to ensure that the subject is given adequate information concerning the study serves a dual function: protection of the subject and documentation that the institution complied with applicable regulations. Informed consent must be obtained in accordance with the informed consent regulation, and any informed consent form used must embody the elements of informed consent required by 21 CFR 50.25. The consent form itself is an aid to ensure that adequate information is provided to the subject. The signed consent form provides documentation of a subject's consent to participate in a study. The entire informed consent process involves giving a subject adequate information concerning the study, providing adequate opportunity for the subject to consider all options, responding to the subject's questions, ensuring that the subject has comprehended this information, and, finally, obtaining the subject's voluntary consent to participate. Informed consent must be documented pursuant to 21 CFR 50.27 and is required for all subjects in clinical investigations of medical devices.

Specific questions may be addressed to the IDE Staff (telephone number above).

Institutional Review Boards (21 CFR 56):

An IRB is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct continuing review of biomedical research involving human subjects in accordance with FDA regulation. The purpose of IRB review is to assure that:

- risks to subjects are minimized, and are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- informed consent will be sought from each prospective subject or the subject's legally authorized representative and will be documented;
- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and
- there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB regulation outlines membership and review requirements. All IRBs must conform to and comply with all requirements in this regulation.

Specific questions may be addressed to the IDE Staff (telephone number above).

Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (21 CFR 58):

The purpose of this regulation is to assure the high quality of nonclinical laboratory testing required to evaluate the safety of medical devices. Sponsors should state in all submissions whether or not nonclinical laboratory tests were conducted in accordance with this regulation. When procedures are not conducted in accordance with the GLP regulation, justifications should be provided.

Specific questions may be addressed to the IDE Staff at (telephone number above).

Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7):

This regulation defines what does and does not constitute valid scientific evidence for the purpose of determination by FDA that there is reasonable assurance that a device is safe and effective for its intended use. Although a 510(k) only requires a demonstration of substantial equivalence to a legally marketed device, this demonstration is in terms of the device being as safe and as effective as a legally marketed device and that the device does not raise different types of questions of safety and effectiveness than the predicate device.

Specific questions about the interpretation of this regulation should be addressed to DOD (telephone number above).

Good Manufacturing Practice for Medical Devices: General (21 CFR 820):

The Good Manufacturing Practice (GMP) for Medical Devices General Regulation, required by section 520(f) of the act, covers the methods used in, and the facilities and controls used for, the design, manufacture, packaging, storage, and installation of devices. It covers the following general areas: organization and personnel; buildings; equipment; controls for components, processes, packaging, and labeling; device holding, distribution, and installation; device evaluation; device and manufacturing records; complaint processing; and quality assurance (QA) system audits.

SMDA amends section 520(f) of the act to authorize the inclusion of preproduction design validation in the GMP regulation. A revised GMP regulation is expected in the near future that incorporates preproduction design controls.

Specific questions on GMP requirements may be addressed to DSMA (telephone number above).

Medical Device Reporting (21 CFR 803):

The Medical Device Reporting (MDR) regulation requires all manufacturers and initial distributors (importers) of medical devices to report to FDA whenever the firms receive or otherwise become aware of information that reasonably suggests that one of their marketed devices: (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that the device or any other similar device would be likely to cause or contribute to a death or serious injury if the malfunction were to reoccur.

Reports of death or serious injury must be telephoned to FDA at (301) 427-7500 no later than 5 calendar days from the time the manufacturer or importer receives the information. Additionally, telephone reports must be followed up by written reports to FDA within 15 working days from the time the manufacturer or importer receives the information for all reports of deaths or serious injuries, and all reports of malfunctions likely to cause or contribute to a death or serious injury.

Manufacturers and importers of devices are required to establish and maintain an MDR file and to permit any authorized FDA employee at reasonable times to have access to, and to copy and verify the records contained in this file. FDA considers any expression of dissatisfaction, be it oral or written, regarding identity, quality, durability, reliability, safety, effectiveness, or performance of a device, to be a complaint. However, not all complaints meet the MDR reporting criteria.

Copies of the MDR regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by contacting DSMA (telephone number above).

Listing and Certification of Color Additives for Foods, Drugs, and Cosmetics (Section 721 of the Act and 21 CFR, Parts 70 through 74):

Section 721 of the act requires that a color additive for use in or on a contact lens in which the color additive comes in direct contact with the eye for a significant period of time must have an applicable final color additive listing regulation in effect before 510(k) clearance of the device can be granted. Batch certification may also be required by the color additive listing regulation. Although the IDE regulation exempts the lenses from section 721 during the study, a sponsor should obtain such listing prior to submitting a 510(k). Section 21 CFR, Parts 70 through 74 are the regulations governing color additives and color additive petitions (CAPs). A CAP should be submitted to the Center for Food Safety and Applied Nutrition (CFSAN) in accordance with 21 CFR 71. Details on submission of a CAP are discussed in this guidance document under the section entitled "COLOR ADDITIVES AND CONTACT LENSES."

Specific questions on color additive listing requirements should be addressed to the Indirect Additives Branch of CFSAN at (202) 254-9511.

Labeling (21 CFR 801):

Class II contact lenses are subject to the general labeling requirements for all medical devices, as outlined in 21 CFR 801. FDA considers all contact lenses to be prescription devices and, therefore, restricts the devices to sale by or on the order of licensed eyecare practitioners. Labeling requirements for prescription devices are discussed in 21 CFR 801.109. Refer to the "LABELING" section in this guidance document for specific information concerning labeling for class II contact lenses.

Management Initiatives:

On June 30, 1993, new policies to improve the device approval process were announced by CDRH. These new policies are as follows:

- Expedited review: To assure that those devices which represent major advancements in medical care reach the market without delay, CDRH has put into effect a "fast track" review system for them. These device applications will be placed in a separate queue and not treated under the usual "first-in, first-reviewed" policy. Included in the expedited review category will be devices used to treat serious conditions for which no alternative treatments exist and devices that offer decidedly greater clinical benefits or lower risks than existing technologies.

- Refuse-to-accept policy: In the past, inadequate and incomplete applications wasted a great deal of CDRH's time. Reviewers were obliged to "re-cycle" these applications, going back to the company repeatedly to request needed information or to clarify poorly presented data. To address this problem, the agency has established a "refuse-to-accept" policy that will specify the minimum criteria for accepting an application. If these are not met, the application will be rejected and returned to the manufacturer.

  Some specific reasons to refuse to accept a 510(k) submission for daily wear contact lenses would be use of an unlisted color (a color without an approved CAP) or submission of a 510(k) for a lens material without an authorized nonproprietary name assigned by the United States Adopted Names (USAN) Council.

- Setting review priorities using risk assessment (previously called "Triage"): Early in the review process, CDRH will determine the potential health hazard posed by each device and will focus most of its attention on those devices that pose a significant risk to patients. Devices with minimal risk potential will receive a less extensive review.

To achieve this, three review tiers have been identified:
Tier I - Essentially a focused labeling review for intended use/indications for use; Tier II - Routine scientific and labeling review (the majority of 510(k)s will be in this tier); and
Tier III - Intensive scientific and labeling review, using a team review approach, for all first and second of a kind devices utilizing new technology or having new intended use(s), as well as other devices determined by their inherent risk to require an intensive review.

Daily wear plastic contact lenses with standard materials, designs, and intended uses, are currently assigned to a Tier II review.

- Status reports to manufacturers: In the past, device manufacturers have often not been able to determine the status of their 510(k) submissions as they proceed through the review system. This has proven a major source of frustration, particularly since lack of information can interfere with sound business planning. To address this problem, CDRH has established a computerized system through which manufacturers will receive a status report on their 510(k) submissions within 3 days of requesting it, if the application has been under review over 90 days.

More information is available on each of these policies in ODE Blue Book memos available by contacting DSMA (telephone number above).

Special Controls:

This guidance document sets forth the special controls which have been determined at this time by CDRH to be necessary to provide reasonable assurance of the safety and effectiveness of class II contact lenses in the absence of an applicable standard. These special controls consist of the recommended protocols for the preclinical and clinical data that FDA believes are necessary to establish substantial equivalence under section 513 of the act. CDRH has carefully considered these recommendations, but also recognizes that it is important to be open-minded about new tests which can be, and are, suggested. If different procedures are chosen by the applicant, a full justification should be submitted. The justification should clearly explain how the alternative procedure can provide the valid scientific evidence needed to demonstrate substantial equivalence. The absence of any justification and supporting evidence may mean that the entire application will be found unacceptable during scientific review.

DOD may be consulted prior to the initiation of any tests if, after reading the guidance document, questions remain concerning a specific test recommendation for a contact lens device (telephone number above).

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