nomax inc

9735 Green Park Industrial Drive
St. Louis, Missouri 63123
(314) 815-5200
Fax (314) 815-5050
www.nomax.com

April 18, 2013

Division of Dockets Management, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Suitability Petition (Expedited Review Requested)
Fluorescein Strips (for ocular examinations)

Dear Sir or Madam,

Nomax, Inc. submits this petition, in quadruplicate, pursuant to 21 CFR 10.30 requesting the Commissioner of the Food and Drug Administration to accept an abbreviated new drug application (ANDA) that includes the same active ingredient as the cited reference listed drug, but differs from the reference listed drug with respect to strength, dosage form and route of administration.

The reference listed drug is a sterile solution that is administered intravenously indicated for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. This diagnostic procedure results in a systemic exposure of 500 mg of fluorescein sodium administered intravenously as a bolus small volume intravenous injection at a rate of 1 mL per second preceding the diagnostic fluorescein angiography procedure. The approved labeling also recommends intradermal injection of 0.05 mL (5 mg of fluorescein sodium) to evaluate for possible allergic reactions to the dye 30 to 60 minutes following administration.

The dosage form for the proposed generic drug consists of 0.6 and 1.0 mg of fluorescein sodium impregnated in sterile strips for professional use in conducting ocular exams. Fluorescein Ocular Strips are a sterilized applicator impregnated with fluorescein (also known as sodium fluorescein) for use in ophthalmic tests. Fluorescein is a weak dibasic acid with a molecular weight of 367 whose sodium salt is used in dilute solution as a dye in the fitting of contact lenses and in the detection of corneal abrasions. Fluorescein is a yellowish-red compound, which fluoresces brilliant yellow-green under ultraviolet or blue illumination. Fluorescein is applied to the surface of the eye by professional practitioners for fitting of contact lenses, disclosing corneal injury, in applantation tonometry and measurement of Fluorescein Breakup Time.

The fine strip, impregnated with fluorescein, a fluorescent dye, is touched to the side of the eye; staining the tear film on the surface of the eye to aid the examination. The dye is naturally cleared from the eye by tears following the examination. This examination is useful in identifying superficial scratches or other problems with the surface of the cornea. It can also reveal foreign bodies on the eye surface and can be used to determine if contact lenses are irritating the surface of the cornea. The dye is applied by moistening the strip with 1 or 2 drops of sterile saline or irrigating solution and then contacting the conjunctiva or fornix as required with moistened

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portion of the strip. The patient is instructed to blink several times after application to distribute the dye throughout the eye.

The use of Fluorescein for the detection of corneal ulcers and abrasions began late in the 19th century. The biology of corneal fluorescein staining began appearing in peer-reviewed literature during the late-1960s and early 1970's and increased during the 80's primarily driven by contact lenses. Numerous studies demonstrated that such minor fluorescein staining occurs in a significant portion of otherwise asymptomatic subjects, and initial work was done on the use of nonclinical models of fluorescein staining. Also, during this period, the role of specific contact lens-related factors in inducing particular fluorescein staining presentations became widely acknowledged, such as the desiccation-based staining observed with thin high-water lenses, staining associated with poor lens fitting, superior epithelial arcuate lesions likely caused by mechanical trauma from lens fitting issues, and the classical pattern of fluorescein staining at the 3 o'clock and 9 o'clock positions commonly seen with rigid gas-permeable lenses.

It should be noted that the approved intravenous solution of Fluorescein Sodium is administered in doses of 500 mg, which represents a systemic dose of 500 times greater than the amount of fluorescein present on a fluorescein strip. In practice, only a fraction of the fluorescein on the strip is transferred to the eye. Likewise, the intradermal administration of 5 mg of fluorescein represents 5 times the amount present on a fluorescein strip.

A. Action Requested

Nomax, Inc is submitting a request for a request for a change in dosage form (from an intravenous solution of fluorescein sodium) to a sterile strip impregnated with fluorescein sodium, a change in strength from a 10% solution (100 mg fluorescein sodium per milliliter) to 0.6 or 1 mg of fluorescein sodium absorbed into a sterile strip, and for a different route of administration (intravenous and intradermal, for the reference listed drug to intraocular instillation for the proposed generic drug. Nomax, Inc. respectfully requests the FDA to consider this request and to issue an approval notification that will allow Nomax to submit an abbreviated new drug application for a generic product that differs from the reference listed drug in the manner described. Nomax also respectfully asks that this request be processed in an expedited manner.

B. Statement of Grounds

The Federal Register history of fluorescein strips has been researched at length and is found to be based on inaccurate information and has ignored several FDA approved products approved under Classification Product Code "KYC" for Fluorescein Strips. Information from the 510(K) database for these three products is provided below. The records in this database clearly indicate that these ophthalmic preparations to be cleared as 510(K) devices.

Table 1 Rose Bengal Ophthalmic Strips

510(K) Number	K810285
Device Name	BARNES-HIND ROSE BENGAL OPHTHALMIC STR.
Applicant	BARNES-HIND, INC.
Classification Product Code	KYC
Date Received	02/02/1981
Decision Date	04/17/1981
Decision	substantially equivalent (SE)
Classification Advisory Committee	Ophthalmic
Review Advisory Committee	General & Plastic Surgery
Type	Traditional
Reviewed by Third Party	No
Combination Product	No

Table 2 Fluorescein Ophthalmic Drops

510(K) Number	K780125
Device Name	FLUORESOFT
Applicant	HOLLES LABORATORIES, INC.
Classification Product Code	KYC
Date Received	01/24/1978
Decision Date	03/15/1978
Decision	substantially equivalent (SE)
Classification Advisory Committee	Ophthalmic
Review Advisory Committee	Ophthalmic
Type	Traditional
Reviewed by Third Party	No
Combination Product	No

Table 3 Fluorescein Ophthalmic Strips

510(K) Number	K831621
Device Name	FLUORETS STERILE OPHTH. STRIPS
Applicant	SMITH & NEPHEW, INC.
Classification Product Code	KYC
Date Received	05/19/1983
Decision Date	07/18/1983
Decision	substantially equivalent (SE)
Classification Advisory Committee	Ophthalmic
Review Advisory Committee	Ophthalmic
Type	Traditional
Reviewed by Third Party	No
Combination Product	No

Federal Register (47 FR 3694, January 28, 1982) included a proposed Classification Product Code, "KYC" for Fluorescein Ophthalmic Strips, as follows.
Section 886.1310: Docket No. 78N-3150: Fluorescein Strip

The Opthalmic Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of fluorescein strips:

1. Identification: A fluorescein strip is a device that is a small strip of filter paper impregnated with fluorescein (a dye use for the diagnosis of certain ocular diseases) used to apply the fluorescein to the surface of the eye.
2. Recommended classification: Class I (general controls). The Panel recommends that there be no exemptions.
3. Summary of reasons for recommendation: The Panel recommends that fluorescein strips be classified into class I because the Panel believes general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. The Panel recommends that this device be packaged sterile.
4. Summary of the data on which the recommendation is based. The Panel based its recommendation on the Panel members knowledge of, and clinical experience with, this device.
5. Risks to health: None identified

FDA agrees with the Panel recommendation and is proposing that fluorescein strips be classified into class I (general controls) with no exemptions. The agency believes that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

§886.1320 Fluroescein strip.

(a) Identification. A fluorescein strip is a device that is a small strip of filter paper impregnated with fluorescein (a dye used for the diagnosis of certain ocular diseases) used to apply the fluorescein to the surface of the eye.

(b) Classification. Class 1 (general controls).

The 510(K) database from which the product information listed in Table 1, Table 2 and Table 3, respectively, clearly shows three products to be approved as substantially equivalent under product classification KYC Fluorescein strips during a 4 year period leading up to the Medical Device Proposal appearing in 47 FR 3694, with one being approved after 47 FR 3694 was published during the review and comment period.

1) Jan-Mar 1978 (K780125) Fluorosoft (fluorescein solution administered as drops).
2) Feb-Apr 1981 (K810285) BARNES-HIND ROSE BENGAL OPHTHALMIC STRIP.
3) May-Jul 1983 (K831621) FLUORETS STERILE OPHTH. STRIPS

However, in an abrupt departure from the proposed classification proposed in 47 FR 3694, January 28, 1982, on September 2, 1987, 33346 Federal Register, Volume 52, No. 170 withdrew proposed §886.1310 for regulating fluorescein strips as a medical device and stated that fluorescein strips would be regulated as a drug in the manner that fluorescein drops are regulated. This FR notice ignores the fact that Fluorsoft (fluorescein drops) had already been approved as a medical device in 1983 and fails to point out that there is no record of a new drug application ever having been FDA approved for fluorescein ophthalmic drops or fluorescein ophthalmic strips. The 1987 Federal Register ignores the existing approval of both fluorescein strips and drops as medical devices, or that all 3 of these products continue to be commercially distributed today as approved medical devices. The 'Drugs@FDA' database or Electronic Orange book does not list any approved or discontinued fluorescein drops or fluorescein strip products. Based on this history, the petitioner is of the opinion that the continued distribution of these three products as KYC substantially equivalent devices is inconsistent with the intent and meaning of FDA reclassification as a drug regulatory ruling published in the 1987 federal register. As such, Nomax questions the regulatory status of the 3 products cleared under KYC, and requests that the FDA review the continued distribution of these 3 products as medical devices or appropriately reclassify fluorescein strip and drop professional products as medical devices.

At the same time, the petitioner points out that a significant number of fluorescein strip products continue to be distributed commercially listed as "other" (unapproved) drugs. This fact is substantiated by products that are drug listed in the old directory of the NDC database as well as for labeling information posted on the DailyMed website (see Table 4 for NDC database search results on fluorescein). The listed data clearly shows that there are no NDA numbers listed for any ophthalmic drops that contain fluorescein as the active ingredient or that contain fluorescein in combination with other active substances. There are also no NDA listings for fluorescein strips. The petitioner finds it hard to understand the federal register notice of 1987 which classified fluorescein strips as drugs that were to be regulated the same as fluorescein drops, particularly when there is no record of fluorescein drops every having been the subject of an NDA submission, much less an NDA approval. Nomax presently distributes fluorescein strips as an unapproved drug and would like to either register the fluorescein strip product under the existing 510(K) classification or file an abbreviated new drug application citing fluorescein injection as a reference listed drug. Since the 1987 federal register notice included a regulatory notification that fluorescein strips were to be regulated as drugs, it appears that an abbreviated new drug application represents a viable pathway forward toward registration. While other firms continue to distribute these products as unapproved drugs, Nomax is well aware of the FDA risk based initiative on continued distribution of unapproved drugs and, in an effort to resolve the regulatory uncertainty surrounding fluorescein strips, is filing this suitability petition based on fluorescein injection as a reference listed drug.

In light of the 1987 federal register notice that rescinded the earlier proposed classification of fluorescein strips as a 510(K) medical device and declares fluorescein strips (and fluorescein drops) will be regulated as drugs, the petitioner proposes to cite NDA approved fluorescein sodium injection as a reference listed drug (see Orange book listing in Appendix 1) for a list of NDA approved fluorescein injection products. This proposal recognizes that fluorescein strips represent a different dosage form and are administered by a different route of administration and Nomax submits a suitability petition requesting FDA agreement to submit an abbreviated new drug application for fluorescein strips. This suitability petition also recognizes there are no approved NDA's for fluorescein drops or fluorescein strips for products presently being distributed commercially and there is no evidence that an NDA was ever submitted or approved.

Justification of this request is based on the fact that fluorescein strips have been used by professional practitioners well over a century to conduct eye examinations, that a very small amount of fluorescein is actually delivered to the eye surface and that the fluorescein is cleared from the eye by tears. This petition also recognizes the FDA determination stated in the 1987 federal register that indicates fluorescein strips will be regulated as drugs. The petitioner submits that citing fluorescein injection as a reference listed drug represents a viable and cost-effective way of submitting an ANDA providing a pathway to register fluorescein strips as drugs.

As further justification, fluorescein, fluorescein sodium, fluorescein drops and fluorescein strips are the subject of monographs in the USP. Copies of these monographs are provided in Appendix 2.

Nomax has also provided proposed draft labeling in Appendix 3. The petitioner proposes to revise this labeling to follow the physician labeling rule format. Notwithstanding the planned revisions, the basic instructions will continue to be directed to professional practitioners and to a large extent will retain similar language and illustrations.

C. *Environmental Impact*

The petitioner claims a categorical exclusion under 21 CFR 25.31

D. *Economic Impact*

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

We respectfully request expedited review of this suitability petition. If you have any questions or comments regarding this submission, please contact me at (865) 274-0101.

Sincerely,

Amanda L Dixon

Amanda Dixon
Director of Regulatory Affairs and Quality
Nomax, Inc
9734 Green Park Industrial Drive
St. Louis, Missouri 63123
Phone: (314) 815-5200
Fax: (314) 815-5050
Email: Amanda@nomax.com

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Div. of Dockets Mgmt HFA-305
FDA
5630 Fishers Lane, Rm 1061
Rockville, MD
20852

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