



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane (HF-7)
Room 14B-03
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

July 19, 2000

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Re: Request for Designation
Trypan Blue Ophthalmic Surgical Marker
Our File: RFD 2000.009

Dear C →

The Food and Drug Administration has completed its review of the request for designation, which you submitted on behalf of Dutch Ophthalmics, USA. The request was filed by this office on May 24, 2000. By mutual agreement, the designation deadline for the request was extended to permit full consideration of the issues raised.

The request seeks jurisdictional classification and assignment of Dutch Ophthalmics' VisionBlue Ophthalmic Surgical Marker (VisionBlue). VisionBlue is a trypan blue dye (0.06%) intended for use in C J surgery. The product formulation is fully described in the request; the product description is incorporated here by reference.

VisionBlue is intended for use to provide "contrast to aid visualization of the capsule C J." According to the request for designation, the product "acts by physically staining the anterior capsule, which renders the capsule visible by providing contrast to the underlying crystalline lens."

Your request recommends that primary review responsibility for VisionBlue be assigned to FDA's Center for Devices and Radiological Health (CDRH). In addition, you suggest that the product be regulated under the medical device provisions of the Federal Food, Drug, and Cosmetic Act (the "Act"). The request argues that VisionBlue is appropriately regulated as a medical device because (1) the product has the physical attributes like those described in the device classification regulation for ophthalmic markers (21 CFR 886.4570); and (2) the product performs a device function. Further, you argue that a number of companies are lawfully marketing ocular and scleral markers as medical devices.

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July 19, 2000
Page 2

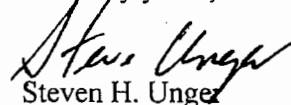
We have carefully considered the information provided in the request, reviewed the pertinent provisions of the Intercenter Agreement (ICA) between CDRH and the Center for Drug Evaluation and Research (CDER), and discussed the issues with senior officials in both centers. Based on our review, we are designating CDER as the agency component with primary jurisdiction for the premarket review and regulation of the product. VisionBlue will be reviewed and regulated under the new drug provisions of the Act, 21 U.S.C. 355. Any clinical investigations of VisionBlue should be conducted under an investigational new drug application in accordance with 21 CFR Part 312.

Our decision is consistent with the jurisdictional classification and assignment of other stains and dyes intended for use in C surgery to assist in the visualization of the capsule. The decision reflects our understanding that the mechanism of action of the product exploits differences in the staining properties of the dye. Specifically, as you note in your request, the staining of the capsule is achieved by "passive diffusion into dead cells or passive adherence to collagenous tissues," whereas "living cells do not actively take up VisionBlue and remain unstained .. ." (Request for Designation at page 9.) We are not aware of any products lawfully marketed as medical devices with a similar mechanism of action.

CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products will be primarily responsible for the premarket review and regulation of VisionBlue. For further information about submission requirements, contact Leslie Vaccari, Supervisory Project Manager, at 301-827-2090.

We understand that you may want to request reconsideration of this jurisdictional decision. Please contact Tracey Forfa, of this office, for guidance on the procedures for requesting reconsideration, or if you want to arrange a meeting to discuss the matter. She can be reached at 301-827-3390.

Sincerely yours,



Steven H. Unger
Product Jurisdiction Officer

cc: Leslie Vaccari



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Office of the Ornbudsman
5600 Fishers Lane (HF-7)
Room 4B-44
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

April 14, 2003

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RE: Request for Reconsideration
VisionBlue® Ophthalmic Solution
Our File: RFD 2000.009

Dear []

The Food and Drug Administration (FDA) has completed its review of the May 3, 2002, Request for Reconsideration you submitted on behalf of Dutch Ophthalmics, USA. Your request seeks reconsideration of our July 19, 2000 decision that VisionBlue is a drug rather than a device. For the reasons described below, we affirm our decision that VisionBlue is a drug.

VisionBlue consists of trypan blue in a buffered sodium chloride solution. Trypan blue is a vital dye; it stains dead cells but not live cells. The product is intended to be used []. The lens has a thin covering known as the lens capsule. [] VisionBlue is placed onto the anterior lens capsule and stains it blue, thus making it easier for the surgeon to see the lens capsule []

[] the patient lies face up on the table. An incision is made in the cornea with a surgical knife. A cannula is placed through the incision and the anterior chamber is filled with air. The purpose of the air bubble is to minimize dilution of VisionBlue by aqueous fluid. VisionBlue is applied as a drop through the cannula directly onto the lens capsule. The lens capsule is quickly stained blue, and the anterior chamber is irrigated to remove excess colorant. The surgeon can then visually identify [] the anterior lens capsule. During surgery, the eye is continually flushed with balanced salt solution, thereby removing any excess VisionBlue. Any residual VisionBlue remaining after cataract surgery is removed through normal aqueous and tear production. Dutch Ophthalmics presented data demonstrating that []

On May 16, 2000, Dutch Ophthalmics submitted a Request for Designation (RFD) requesting classification of VisionBlue as a device. This RFD stated, among other things, that the staining of the lens capsule is achieved by "passive adherence to collagenous tissues," whereas "living cells do not actively take up VisionBlue and remain

unstained...." FDA's initial designation letter, dated July 19, 2000, concluded that VisionBlue is a drug, stating that we were not aware of any products lawfully marketed as medical devices that exploit a differential staining property similar to the one described for VisionBlue.

On May 3, 2002, Dutch Ophthalmics requested reconsideration of the initial designation decision. The essence of the request for reconsideration is Dutch Ophthalmics' assertion that the agency erred in its conclusion that VisionBlue exploits the differential staining characteristics of trypan blue. According to the request for reconsideration, VisionBlue achieves its primary intended purpose by physical intercalation with the anterior lens capsule's three-dimensional collagenous structure, and not by either chemical or metabolic action. The request for reconsideration explains the company's intercalation theory. It states that because of the

large size of the dye molecule relative to the open three-dimensional structure of collagen, trypan blue molecules can become physically entangled within and temporarily mark the tissue.

The request for reconsideration also notes that the lens capsule is completely devoid of cells, living or dead, and then asserts that differential staining is neither necessary nor even possible for VisionBlue's intended use. Therefore, according to the request for reconsideration, Dutch Ophthalmics claims that VisionBlue meets the definition of a device contained in 21 U.S.C. § 201(h).

Moreover, according to the request for reconsideration, the classification of VisionBlue as a drug creates a significant disparity between VisionBlue and other ophthalmic surgical markers containing vital dyes (e.g., gentian violet and methylene blue). According to the request for reconsideration, the

use of dyes as ophthalmic surgical markers is so uncontroversial that FDA long ago classified them as devices *exempt* from the 510(k) premarket notification process (21 CFR § 886.4570).... In contrast, FDA's designation of VisionBlue ... as a drug means that this functionally indistinguishable product will be regulated under the new drug application (NDA) process.

The request for reconsideration states that this regulatory scheme would impose a significant and unfair competitive disadvantage on Dutch Ophthalmics with no articulated scientific basis.

We have reviewed all the information you submitted, met with you, and consulted with officials in the Center for Drug Evaluation and Research (CDER), the Center for

Devices and Radiological Health (CDRH) and the Office of Chief Counsel.¹ For the reasons described below, we affirm our previous determination and are classifying VisionBlue as a drug.

First, VisionBlue meets the definition of a drug contained in the Federal Food, Drug, and Cosmetic Act at 21 U.S.C. 321(g). It is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man; and/or an article intended to affect the structure or any function of the body.

Second, VisionBlue has not been shown to achieve its primary intended purpose without chemical action within the body. Thus, although VisionBlue clearly meets the definition of a drug, it has not been shown that it meets the definition of a device.

The request for reconsideration asserts that VisionBlue stains the lens capsule by physical intercalation, and describes intercalation as the large VisionBlue molecules becoming physically entangled within the three dimensional structure of collagen and temporarily marking the tissue.² FDA believes that the science of intercalation is new

¹ On February 13, 2002, officials from CDRH, CDER, Office of Chief Counsel, and the Ombudsman's Office met with representatives of Dutch Ophthalmics to discuss the feasibility of the company submitting a Request for Reconsideration. Dutch Ophthalmics submitted additional information via electronic mail on September 24, 2002, and October 28, 2002. Numerous telephone conversations also took place between counsel for Dutch Ophthalmics and the Ombudsman's Office while this Request for Reconsideration was being reviewed.

² The Request for Reconsideration contains a detailed statement of Dutch Ophthalmics' conclusion that VisionBlue does not stain the lens capsule through chemical action. Among other things, this statement concludes that VisionBlue could not stain the lens capsule by hydrogen bonding because, when solubilized in an aqueous solution at a neutral pH, VisionBlue does not contain any charged atomic constituents that could serve to either accept or donate hydrogen atoms for the formation of hydrogen bonds. (VisionBlue's pH is 7.4.) A further discussion of the possibility of hydrogen bonding was prompted by a statement in a reference Dutch Ophthalmics submitted with the Request for Reconsideration that dyes such as trypan blue stain "apparently by hydrogen bonding rather than by anionic salt unions as with ordinary cytoplasmic structures..." (Lillie RD, Fullmer HM, (eds): Histopathologic Technic and Practical Histochemistry, 4th ed. New York, McGraw-Hill Book Company pp. 140-144.)

The subsequent discussion included an analysis of a study showing that VisionBlueC

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and imprecise; the current literature is not definitive as to whether the process is physical or chemical. Even if intercalation is a purely physical process, however, it would not be clear that VisionBlue meets the definition of a device because the primary intended purpose of VisionBlue is not simply to stain the lens capsule. The primary intended purpose of VisionBlue is to stain the lens capsule and at the same time, **not** stain the lens.³ It is by staining the lens capsule -- and only the lens capsule -- that VisionBlue enables the surgeon to see the lens capsule. The inability of VisionBlue to stain the live cells in the lens is likely due to some kind of chemical action.

Dutch Ophthalmics asserts in response that the lens remains unstained not because of the characteristics of VisionBlue, but because of the characteristics of the lens capsule, which physically prevents VisionBlue from coming into contact with the lens. In a telephone conversation, counsel for Dutch Ophthalmics analogized the lens capsule to the shell of a hard boiled egg. When a hard boiled egg is dyed, the egg itself is not dyed because the shell prevents the dye from coming into contact with the egg. In this conception of VisionBlue's mechanism of action, trypan blue's differential staining characteristics would be irrelevant.

We acknowledge that initially the lens capsule could prevent VisionBlue from staining the lens by acting as a physical barrier between VisionBlue and the lens. However, as Dutch Ophthalmics' description of the use of VisionBlue makes clear, some VisionBlue remains in the anterior chamber.

⁴ In addition, as made clear by the video submitted with the initial RFD, the

Thus, we conclude that VisionBlue does exploit its differential staining characteristic to accomplish its primary intended purpose.

The information provided to FDA does not explain how VisionBlue stains dead cells and tissue with no cells at all, but does not stain live cells. Nevertheless, we

As explained above, FDA concludes that the intended purpose of VisionBlue is to stain the lens capsule while not staining the lens. Whether or not VisionBlue stains the lens capsule through hydrogen bonding, the agency concludes that the fact that VisionBlue does not stain the non-capsular portion of the lens is due to chemical action of some sort.

³ In a e-mail dated September 24, 2002, counsel for Dutch Ophthalmics stated that the intended use of VisionBlue is to allow the surgeon "to distinguish the lens capsule from the underlying lens mass."

⁴ The initial RFD, dated May 16, 2000, states on page 10 that "During surgery the eye is continually flushed with balanced salt solution, thereby removing any excess VisionBlue. The duration of use is typically the time of surgery, which normally takes place in 30 minutes or less. Any residual VisionBlue is removed through normal aqueous and tear production post surgery."

believe this differential staining characteristic entails chemical action of some kind. Therefore, we conclude that that VisionBlue achieves its primary intended purpose through chemical action within the body. Accordingly, we conclude that VisionBlue has not been shown to meet the definition of a device.

Third, VisionBlue does not fit within the generic type of device "ophthalmic surgical marker" covered by 21 CFR § 886.4570. This classification only applies to medical devices and VisionBlue is a drug. Even if VisionBlue were a device, it would not be covered by this classification. Devices covered by this classification regulation are intended for use in marking the cornea, sclera, or exterior surface of the eye to show where a surgical incision should be made. VisionBlue, in contrast, is applied intraocularly for a very different purpose, as described above. While both VisionBlue and some of the marking pens included in this classification use vital dyes (gentian violet and methylene blue), that does not, by itself, mean that VisionBlue fits within that classification.

Finally, the FDA's decision that VisionBlue is a drug is consistent with past agency decisions. We are aware of no product legally marketed as a device that is intended to mark or dye the inside of the eye. For example, we have previously classified fluorescein strips as a drug. Fluorescein sodium is another vital dye. It is available in ophthalmic strips indicated for staining the anterior segment of the eye when delineating a corneal injury, herpetic lesion or foreign body, or determining the site of an intraocular injury. The fluorescein impregnated strips are placed on the eye until adequate staining is achieved. In the Federal Register of November 8, 1986, fluorescein strips were classified as drugs.

For these reasons (VisionBlue meets the statutory definition of a drug, VisionBlue has not been shown to meet the statutory definition of a device, VisionBlue does not fit within the description of products covered by 21 CFR § 886.4570, and the agency regulates other vital dyes intended for use inside the eye as drugs), we affirm our previous decision and conclude that VisionBlue is a drug.

CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAOPD) will be responsible for the premarket review and regulation of VisionBlue. For further information, contact Lori Gorski, Project Manager, Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, 9201 Corporate Boulevard, HFD-550, Rockville, MD 20850 or at 301-827-2090.

Dutch Ophthalmics, USA
April 14, 2003
Page 6

As you know, you may request supervisory review of this decision under 21 CFR § 10.75. If you have any other questions about this letter, or wish to discuss the matter further with the Ombudsman's Office, please contact me at 301-827-3390.

Sincerely,

A handwritten signature in cursive script, appearing to read "Suzanne O'Shea".

Suzanne O'Shea
Product Jurisdiction Officer

cc: Lori Gorski