U.S. Department of Health & Human Services

Food and Drug Administration

SAVE REQUEST

USER:	(jrc)
FOLDER:	K123169 - 389 pages
COMPANY:	FORWARD SCIENCE LLC (FORWSCIE)
PRODUCT:	DIAGNOSTIC LIGHT, SOFT TISSUE DETECTOR (NXV)
SUMMARY:	Product: ORALID
DATE REQUESTED:	Feb 19, 2014
DATE PRINTED:	Feb 19, 2014
Note:	Printed

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

K123769

V. 510(k) SUMMARY

MAR 13 2013

Submitted by: Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

Contact Person: Brian Pikkula, PhD

Date Prepared: October 04, 2012

Proprietary Name: OralID™

Common Name: Oral Examination Light and Accessories

Classification:

Class II:	21 CFR § 872.6350
Class I: (Exempt)	21 CFR § 886.5850

Classification Name: Ultra-violet Detector – NXV (EAQ)
Photosensitive glasses – HQY (Exempt)

Predicate Devices: DentLight Oral Exan Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

Device Description:

OralID™ is a battery operated (CR123A), hand-held, oral illumination and examination light designed for use by dental and medical professionals to be used as an adjunctive tool for fluorescence visualization of oral mucosal tissue. OralID™ accessories include two pair of filtered eyewear for both the clinician and patient.

Intended Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Technological Characteristics:

OralID™ uses "CR123A" batteries to operate one high intensity LED to emit a visible blue light to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer. While using the filtered glasses and OralID™ oral examination light, healthy tissue fluoresces while abnormal tissue appears dark due to lack of fluorescence.

Substantial Equivalence

OralID™ has the same intended use and technical characteristics as the predicate devices (K101140 and K102083); each uses fluorescence as the primary mode to aid in visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces a violet light and views fluorescence through filtered loupes.

Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens.

OralID™ uses "CR123A" batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk of the recharging process.

The operational principles of the proposed and predicate devices are identical with the primary mode to aid in visualization of tissue through fluorescence. Each of these devices is powered by batteries and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

Performance Testing and Compliance

The following tests were conducted to evaluate the functionality and performance of the proposed OralID™ oral examination light:

- Optical Safety
- Thermal Safety
- Optical Wavelength
- Optical Power Testing
- Beam Quality

OralID™ conforms to electrical safety requirements and complies with the electromagnetic compatibility standards established by IEC 60601-1-2.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 13, 2013

Dr. Brian Pikkula
President & CTO
Forward Science LLC
2511 Wind Fall Lane
SUGAR LAND TX 77479

Re: K123169
Trade/Device Name: OralID™
Regulation Number: 21 CFR 872.6350
Regulation Name: Ultraviolet Detector
Regulatory Class: II
Product Code: NXV
Dated: February 6, 2013
Received: February 11, 2013

Dear Dr. Pikkula:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kwame O. Ulmer for

Anthony D. Watson, B.S., M.S., M.B.A.
Director
Division of Anesthesiology, General Hospital,
Respiratory, Infection Control and
Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): K123169

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

Prescription Use____X____ AND/OR Over-the-Counter_____
(Per 21 CFR 801 Subpart D) (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Susan Runner, DDS, MA
Mary S. Runner -S
2013.03.13
13:22:37 -04'00'

(Division Sign-Off)
Division of Anesthesiology, General Hospital Infection Control, Dental Devices

510(k) Number: K123169

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 13, 2013

Dr. Brian Pikkula
President & CTO
Forward Science LLC
2511 Wind Fall Lane
SUGAR LAND TX 77479

Re: K123169
Trade/Device Name: OralID™
Regulation Number: 21 CFR 872.6350
Regulation Name: Ultraviolet Detector
Regulatory Class: II
Product Code: NXV
Dated: February 6, 2013
Received: February 11, 2013

Dear Dr. Pikkula:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kwame O. Ulmer for

Anthony D. Watson, B.S., M.S., M.B.A.
Director
Division of Anesthesiology, General Hospital,
Respiratory, Infection Control and
Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Concurrence & Template History Page
[THIS PAGE IS INCLUDED IN IMAGE COPY ONLY]

Full Submission Number: K123169

For Office of Compliance Contact Information:

http://insideportlets.fda.gov:9010/portal/page?_pageid=197,415881&_dad=portal&_schema=PORTAL&org=318

For Office of Surveillance and Biometrics Contact Information:

http://insideportlets.fda.gov:9010/portal/page?_pageid=197,415881&_dad=portal&_schema=PORTAL&org=423

Digital Signature Concurrence Table	
Reviewer Sign-Off	Leah S. Royce -S 2013.03.13 12:30:59 -04'00'
Branch Chief Sign-Off	Mary S. Runner -S 2013.03.13 13:24:18 -04'00'
Division Sign-Off	Kwame O. Ulmer -S 2013.03.13 14:49:54 -04'00'

Template Name: K1(A) – SE after 1996

Template History:

Date of Update	By	Description of Update
7/27/09	Brandi Stuart	Added Updates to Boiler Table
8/7/09	Brandi Stuart	Updated HFZ Table
1/11/10	Diane Garcia	Liability/Warranty sentence added at bottom of 1st page
10/4/11	M. McCabe Janicki	Removed IFU sheet and placed in Forms
9/25/12	Edwena Jones	Added digital signature format
12/12/12	M. McCabe Janicki	Added an extra line between letter signature block and the word "Enclosure". Also, added a missing digit in 4-digit extension on letterhead zip code: "002" should be "0002".

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): K123169

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

Prescription Use____X____ AND/OR Over-the-Counter_____
(Per 21 CFR 801 Subpart D) (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Mary S. Runner -S
Susan Runner DDS, MA 2013.03.13
13:22:37 -04'00'

(Division Sign-Off)
Division of Anesthesiology, General Hospital Infection Control, Dental Devices

510(k) Number: K123169

K123169 V.1

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 11, 2012

FORWARD SCIENCE LLC
2511 WIND FALL LN
SUGAR LAND, TEXAS 77479
ATTN: BRIAN PIKKULA

510k Number: K123169
Product: ORALID
On Hold As of 12/7/2012

We are holding your above-referenced Premarket Notification (510(k)) for 30 days pending receipt of the additional information that was requested by the Office of Device Evaluation. Please remember that all correspondence concerning your submission MUST cite your 510(k) number and be sent in duplicate to the Document Mail Center at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official premarket notification submission. Also, please note the new Blue Book Memorandum regarding Fax and E-mail Policy entitled, "Fax and E-Mail Communication with Industry about Premarket Files Under Review. Please refer to this guidance for information on current fax and e-mail practices at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm.

The deficiencies identified represent the issues that we believe need to be resolved before our review of your 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm.

In accordance with 21 CFR 807.87(l), FDA may consider a 510(k) to be withdrawn if the submitter fails to provide additional information within 30 days of an Additional Information (AI) request. FDA generally permits submitters additional time to respond to such requests. FDA intends to automatically grant a maximum of 180 calendar days from the date of the AI request, even if the submitter has not requested an extension. Therefore, submitters are no longer required to submit written requests for extension. However, submitters should be aware that FDA intends to issue a notice of withdrawal under 21 CFR 807.87(l) if FDA does not receive, in a submission to the appropriate Document Control Center, a complete response to all of the deficiencies in the AI request within 180 calendar days of the date that FDA issued that AI request. In this instance, pursuant to 21 CFR 20.29, a copy of your 510(k) submission will remain in the Office of Device Evaluation. If you then wish to resubmit this 510(k) notification, a new number will be assigned and your submission will be considered a new premarket notification submission.

For further information regarding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee Amendments of 2012 (MDUFA III), to the Federal Food, Drug, and Cosmetic Act, you may refer to our guidance document entitled "Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals". You may review this document at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm>.

Please remember that the Safe Medical Devices Act of 1990 states that you may not place this device into commercial distribution until you receive a decision letter from FDA allowing you to do so.

If you have procedural questions, please contact the Division of Small Manufacturers International and Consumer Assistance (DSMICA) at (301)796-7100 or at their toll-free number (800)638-2041, or contact the 510k staff at (301)796-5640.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification Section
Office of Device Evaluation
Center for Devices and Radiological Health

Mawii, Lal Pek *

From: Microsoft Outlook
To: BPIKKULA@ORALID.COM
Sent: Tuesday, December 11, 2012 3:29 PM
Subject: Relayed: K123169 - hold letter

Delivery to these recipients or groups is complete, but no delivery notification was sent by the destination server:

BPIKKULA@ORALID.COM (BPIKKULA@ORALID.COM)

Subject: K123169 - hold letter

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name [signature]

Subject: 510(k) Number K123467

To: The Record

Please list CTS decision code TH

- ☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)
- ☐ Hold (Additional Information or Telephone Hold).
- ☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*		
510(k) Summary /510(k) Statement	*Attach Summary*		
Truthful and Accurate Statement.	*Must be present for a Final Decision*		
Is the device Class III?			
If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)			
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			
Is this device intended for pediatric use only?			
Is this a prescription device? (If both prescription & OTC, check both boxes.)			
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			
Is clinical data necessary to support the review of this 510(k)?			
For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was			

conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)

Does this device include an Animal Tissue Source?

All Pediatric Patients age<=21

Neonate/Newborn (Birth to 28 days)

Infant (29 days -< 2 years old)

Child (2 years -< 12 years old)

Adolescent (12 years -< 18 years old)

Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)

Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)

Nanotechnology

Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html) *Contact OC.*

Regulation Number	**Class***	**Product Code**

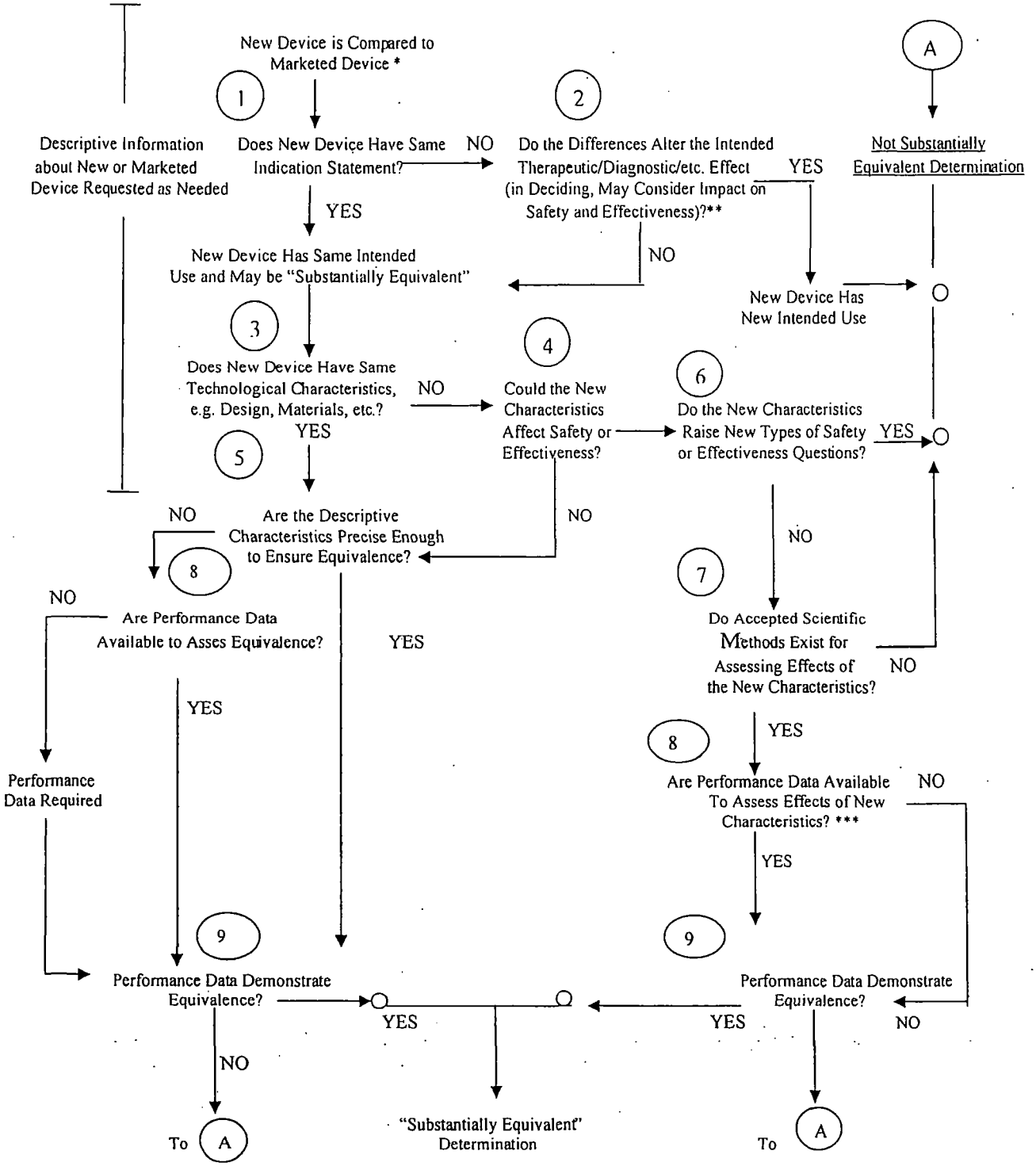
(*If unclassified, see 510(k) Staff)

Additional Product Codes:

Review: Susan Runner (Branch Chief) DE03 (Branch Code) 12/7/12 (Date)

Final Review: Susan Runner (Division Director) 12/7/12 (Date)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Premarket Notification [510(k)] Review
Traditional

K123169
Telephone Hold

Date: December 7, 2012

To: The Record Office: ODE

From: Leah S. Royce, D.D.S. Division: DAGRID

510(k) Holder: Forward Science LLC

Device Name: Oral ID

Contact: Brian Pikkula, Ph.D.

Phone: 855-696-7254

Fax: 855-329-6725

Email: bpikkula@oralid.com

I. Purpose and Submission Summary

The 510(k) holder would like to introduce Oral ID into interstate commerce. Oral ID is a class II medical device that is regulated under 21CFR872.6350 as an ultraviolet detector which is a device intended to provide a source of ultraviolet light which is used to identify otherwise invisible material such as dental plaque, present in or on teeth, under product code NXV. Oral ID accessories include photosensitive glasses (21 CFR 886.5859, HQY) which are class I exempt. The company has identified the following predicate devices: VELscope Vx (K102083) and Dentlight Oral Exam Light Kit (K101140).
The submission includes a medical device user fee cover sheet, a confirmation of payment document, a CDRH premarket review submission cover sheet, a table of contents, a 510(k) cover letter, general information, indications for use statement (IFUS), 510(k) Summary, Truthful and Accuracy Statement, Class III Summary and Certification statement, Financial Certification or Disclosure Statement, Declaration of Conformity, Executive Summary, Device description and specifications, substantial equivalence, proposed labeling, sterilization/shelf life statement, biocompatibility, software statement, electromagnetic compatibility/electrical summary, performance testing-bench, performance testing -

animal, and performance testing - clinical statement. The RTA checklist was completed and sent to the company, and responses were provided by email on November 7th.

The submission references the following standards, however no SDRs were provided

- IEC 60601 and "collateral standards"
- ISO 13485 and ISO 14971

On November 7th, the company provided additional information in response to the RTA checklist and comments.

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	x		
Truthful and Accuracy Statement	x		
510(k) Summary or 510(k) Statement Summary	x		
Standards Data Report Form – Form 3654 1: No standard used - No Standards Form Required 2: Declaration of Conformity - Yes Standards Form Required 3: Standard but no declaration - Yes Standards Form Required		x	

The 510(k) Summary includes the IFUS, technological characteristics contains a claim in the second paragraph which will need to be modified or removed, substantial equivalence discussion is adequate. No performance testing is included.

III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		x	
Is the device an implant (implanted longer than 30 days)?		x	
Does the device design use software?		x	
Is the device sterile?		x	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?	x		

The submission states that the device is a hand-held, battery operated, oral illumination and examination light, with accessories of filtered glasses for use by the user and the patient. It appears that the photosensitive glasses are included in the submission.

The light:

(b) (4)

[redacted]

The submission states that when healthy tissue is exposed to the blue light and the end user will

view the tissue as green through the photosensitive glasses as the healthy tisse will emit fluorescence. The submission states that under identical conditions, abnormal tissue will appear dark due to lack of fluorescence. (b) (4)

(b) (4)

(b) (4)

Accessories:

(b) (4)

IV. Indications for Use

Oral ID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

Oral ID ™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence.

(b) (4)

Oral ID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the Oral ID blue light.

(b) (4)

V. Predicate Device Comparison

The submission device differs from the predicate devices in the power source. The submission device uses primary CR123A batteries, whereas the predicate devices use rechargeable batteries. All devices use batteries to power a high -intensity LED that produce light as illumination for excitation for tissue fluorescence viewed through a filtered lens.

Comparison of Submission Device with Predicates:

	OralID Forward Science	VELscope Vx	Dentlight Oral Exam Light Kit
Submission number	K123169	K102083	K101140
Indications for use statement	Oral ID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia. (b) (4) (b) (4) .....eyewear is reusable ...	VELscope Vx is intended to be used by a dentist or health-care provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia. VELscope Vx is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus ais in determining the appropriate margin for surgical excision.	Dentlight Oral Exam Light Kit is indicated for providing illumination to aid visualization during oral procedures and an adjunct to enhance the visualization for oral examination of mucosal abnormalities
Power source for LED	CR 123A primary lithium batteries	Rechargeable Lithium ion batteries	Rechargeable lithium battery
Method of operation	Direct visualization of fluorescent tissues	Direct visualization of fluorescent tissues	Direct visualization of fluorescent tissues
Wavelength Light intensity Projected light image	(b) (4)	400-460 nm blue light .75 W 4 cm at 10 cm distance	410nm violet light 530 nm green light 6000K (white) 30 – 75 mW/cm2

Clinical data		Photographs of a variety of oral mucosal lesions	Illumination and fluorescent image
Bench testing	(b) (4)	Spectral data...	Optical power testing
	Peak Wavelength nm		Optical wavelength
Cycle time recommended for use Operating temperature			Beam quality 5,10,20 seconds 0 – 35 degrees
Standards conformance	Referenced 60601		IEC 60601-1-2
Accessories	Two pair filtered glasses		

VI. Labeling

The draft labeling includes the manufacturer address, name, contents, symbols with English translation, and the Directions for Use (DFU) includes adequate device description, intended uses identical to the IFUS, appropriate warnings regarding care and storage, selection of batteries, and a caution not to look directly into the light. (b) (4)

(b) (4)

VII. Sterilization/Shelf Life/Reuse

The submission states that sterilization and shelf life are not applicable. However the DFU includes a section on maintenance stating that the device "should be cleaned and disinfected between each patient use. The external surfaces of the Handpiece should be wiped down with a hospital grade surface disinfectant and a towlette or gauze...do not use disinfectants .with alcohol content over 70%". (b) (4)

(b) (4)

VIII. Biocompatibility

(b) (4)

IX. Software

The submission states that this section is not applicable. It appears that the device does not use software.

Version:		
Level of Concern:		
	Yes	**No**
Software description:		
Device Hazard Analysis:		
Software Requirements Specifications:		
Architecture Design Chart:		
Design Specifications:		
Traceability Analysis/Matrix:		
Development:		
Verification & Validation Testing:		
Revision level history:		
Unresolved anomalies:		

X. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

(b) (4)

[redacted]

XI. Performance Testing – Bench

(b) (4)

[redacted]

(b) (4) [redacted]

XII. Performance Testing – Animal

The submission does not include any performance testing using animals.

XIII. Performance Testing - Clinical

(b) (4) [redacted]

XIV. Substantial Equivalence Discussion

	Yes	No	
1. Same Indication Statement?		x	If **YES** = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NSE**
3. Same Technological Characteristics?		x	If **YES** = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?		x	If **YES** = Go To 6
5. Descriptive Characteristics Precise Enough?			If **NO** = Go To 8 If **YES** = Stop **SE**
6. New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NSE**
7. Accepted Scientific Methods Exist?			If **NO** = Stop **NSE**
8. Performance Data Available?			If **NO** = Request Data
9. Data Demonstrate Equivalence?			Final Decision:

Note: See http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

1. Explain how the new indication differs from the predicate device's indication:

2. Explain why there is or is not a new effect or safety or effectiveness issue:

3. Describe the new technological characteristics:

4. Explain how new characteristics could or could not affect safety or effectiveness:

5. Explain how descriptive characteristics are not precise enough:

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:

7. Explain why existing scientific methods can not be used:

8. Explain what performance data is needed:

9. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

XV. Contact History

(b) (4) [redacted]

1. (b) (4) [redacted]

(b) (4) [redacted]

2. (b) (4) [redacted]

(b) (4)

3. (b) (4)

4. (b) (4)

5. (b) (4)

6. (b) (4)

(b) (4)

7. (b) (4)

8. (b) (4)

9.

10. (b) (4)

11. (b) (4)

12. (b) (4) [redacted]

XVI. (b) (4) [redacted]

Digital Signature Concurrence Table	
Reviewer Sign-Off	Leah S. Royce 2012.12.07 15:25:24 -05'00'
Branch Chief Sign-Off	Susan Runner DDS, MA 2012.12.07 16:04:43 -05'00'
Division Sign-Off	Susan Runner DDS, MA 2012.12.07 16:07:37 -05'00'

(b) (4) Email of completed review of submission

(b) (4) Email of completed review of submission

(b) (4) Email of completed review of submission

(b) (4) Email of completed review of submission

(b) (4) Email of completed review of submission

(b) (4) Email of completed review of submission

Payne, Melissa T*

From: Microsoft Outlook
To: bpikkula@oralid.com
Sent: Thursday, October 11, 2012 12:36 PM
Subject: Relayed: K123169 FDA Ack Letter/ E-Copy Attachment

Delivery to these recipients or groups is complete, but no delivery notification was sent by the destination server:

bpikkula@oralid.com (bpikkula@oralid.com)

Subject: K123169 FDA Ack Letter/ E-Copy Attachment

FORWARD SCIENCE LLC

2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Cell: 832-526-0150

Food and Drug Administration
CDRH/ODE
Document Mail Center (HFZ-401)
9200 Corporate Blvd
Rockville, MD 20850

November 7, 2012

RE: Reply to K123169 - 510(k) RTA Checklist

Dr. Leah S. Royce,

(b) (4)

[redacted]

If you have any questions regarding this Reply, please contact me by phone at 832-526-0150 or by email at bpikkula@oralid.com.

Sincerely Yours,

Brian Pikkula. Ph.D.
President & CTO
Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Cell:832-526-0150
bpikkula@oralid.com

FORWARD SCIENCE LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Cell: 832-526-0150

Table of Contents

FORWARD SCIENCE LLC

2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Cell: 832-526-0150

Section A7: If submission relies upon a national or international standard as part of demonstration of substantial equivalence, submission contains Standards Data Report for 510(k)s (FDA Form 3654) or includes detailed information about how and the extent to which the standard has been followed.

(b) (4)

[redacted]

Section A10: The submission identifies prior submissions for the same device for which FDA provided feedback related to the data or information needed to support substantial equivalence (e.g., submission numbers for Pre- Submission, IDE, prior not substantially equivalent (NSE) determination, prior 510(k) that was deleted or withdrawn) or states that there were no prior submissions.

There have been no prior submissions for the OralID device.

Section E23: Full test report is provided for each completed test to explain how the data generated from the test supports a finding of substantial equivalence. (A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), predefined pass/fail criteria, results summary, and conclusions.).

(b) (4)

[redacted]

FORWARD SCIENCE LLC

2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Cell: 832-526-0150

Section E25: If literature was used as performance data, submission includes reprints or a summary of each article, and a discussion as to how each article is applicable to support the substantial equivalence of the subject device to the predicate.

(b) (4)

[redacted]

FORWARD SCIENCE LLC

2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Cell: 832-526-0150

(b) (4)

[redacted]

Section J35: **Submission includes evaluation of electromagnetic compatibility per IEC 60601-1-2 or equivalent FDA-recognized standard and if applicable, the device-specific standard**
OR
submission includes electromagnetic compatibility evaluation using methods or standards that are not FDA-recognized and information indicating that these methods/standards otherwise meet applicable statutory and regulatory requirements.

(b) (4)

[redacted]

(b) (4) Optical Power & Wavelength

(b) (4) Optical Power & Wavelength

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

October 11, 2012

FORWARD SCIENCE LLC
2511 WIND FALL LN
SUGAR LAND, TEXAS 77479
ATTN: BRIAN PIKKULA

510k Number: K123169

Received: 10/9/2012

Product: ORALID

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification, (510(k)), you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product and for the above referenced 510(k) submitter. Please note, if the 510(k) submitter is incorrect, please notify the 510(k) Staff immediately. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. We will notify you when the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official 510(k) submission.

On September 27, 2007, the President signed an act reauthorizing medical device user fees for fiscal years 2008 - 2012. The legislation - the Medical Device User Fee Amendments of 2007 is part of a larger bill, the Food and Drug Amendments Act of 2007. Please visit our website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm
for more information regarding fees and FDA review goals. In addition, effective January 2, 2008, any firm that chooses to use a standard in the review of ANY new 510(k) needs to fill out the new standards form (Form 3654) and submit it with their 510(k). The form may be found at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new section 402(j) (42 U.S.C. § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm accompany 510(k)/HDE/PMA submissions. The agency has issued a draft guidance titled: "Certifications To Accompany Drug, Biological

Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134034.htm. According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

Please note the following documents as they relate to 510(k) review: 1) Guidance for Industry and FDA Staff entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs and BLA Supplements". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm. Please refer to this guidance for information on a formalized interactive review process. 2) Guidance for Industry and FDA Staff entitled, "Format for Traditional and Abbreviated 510(k)s". This guidance can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm. Please refer to this guidance for assistance on how to format an original submission for a Traditional or Abbreviated 510(k).

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.html. In addition, the 510(k) Program Video is now available for viewing on line at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm .

Please ensure that whether you submit a 510(k) Summary as per 21 CFR 807.92, or a 510(k) Statement as per 21 CFR 807.93, it meets the content and format regulatory requirements.

Lastly, you should be familiar with the regulatory requirements for medical devices available at Device Advice http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have questions on the status of your submission, please contact DSMICA at (301)796-7100 or the toll-free number (800)638-2041 , or at their internet address http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. If you have procedural questions, please contact the 510(k) Staff at (301)796-5640.

Sincerely,

510(k) Staff

VOLUME I

Form Approved: OMB No. 0910-511 Expiration Date: February 28, 2013. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **MEDICAL DEVICE USER FEE COVER SHEET**	PAYMENT IDENTIFICATION NUMBER: (b) (4) Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)	2. CONTACT NAME
FORWARD SCIENCE LLC 2511 Wind Fall Lane Sugar Land TX 77479 US	Brian Pikkula 2.1 E-MAIL ADDRESS bpikkula@oralid.com 2.2 TELEPHONE NUMBER (include Area code) 855-696-7254 2.3 FACSIMILE (FAX) NUMBER (Include Area code) 855-329-6725
1.1 EMPLOYER IDENTIFICATION NUMBER (EIN) (b) (4)	

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/oc/mdufma

Select an application type:	3.1 Select a center
[X] Premarket notification(510(k)); except for third party	[X] CDRH
[ ] 513(g) Request for Information	[ ] CBER
[ ] Biologics License Application (BLA)	3.2 Select one of the types below
[ ] Premarket Approval Application (PMA)	[X] Original Application
[ ] Modular PMA	Supplement Types:
[ ] Product Development Protocol (PDP)	[ ] Efficacy (BLA)
[ ] Premarket Report (PMR)	[ ] Panel Track (PMA, PMR, PDP)
[ ] Annual Fee for Periodic Reporting (APR)	[ ] Real-Time (PMA, PMR, PDP)
[ ] 30-Day Notice	[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)

[ ] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA

[X] NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number:

5. FDA WILL NOT ACCEPT YOUR SUBMISSION IF YOUR COMPANY HAS NOT PAID AN ESTABLISHMENT REGISTRATION FEE THAT IS DUE TO FDA. HAS YOUR COMPANY PAID ALL ESTABLISHMENT REGISTRATION FEES THAT ARE DUE TO FDA?

[X] YES (All of our establishments have registered and paid the fee, or this is our first device, and we will register and pay the fee within 30 days of FDA's approval/clearance of this device.)
[ ] NO (If "NO," FDA will not accept your submission until you have paid all fees due to FDA. This submission will not be processed; see http://www.fda.gov/cdrh/mdufma for additional information)

6. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

[ ] This application is the first PMA submitted by a qualified small business, including any affiliates	[ ] The sole purpose of the application is to support conditions of use for a pediatric population
[ ] This biologics application is submitted under section 351 of the Public Health Service Act for a product licensed for further manufacturing use only	[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

7. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).
[ ] YES [X] NO

PAPERWORK REDUCTION ACT STATEMENT
Public reporting burden for this collection of information is estimated to average 18 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the address below.

Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, 4th Floor Rockville, MD 20850
[Please do NOT return this form to the above address, except as it pertains to comments on the burden estimate.]

8. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION

$4,960.00 04-Oct-2012

Form FDA 3601 (01/2007)

"Close Window" Print Cover sheet

Online Payment

Step 3: Confirm Payment **1 | 2 | 3**

Thank you.
Your transaction has been successfully completed.

Pay.gov Tracking Information

Application Name: FDA User Fees
Pay.gov Tracking ID: 25870U3J
Agency Tracking ID: 6064405
Transaction Date and Time: 10/04/2012 22:11 EDT

Payment Summary

Address Information	Account Information	Payment Information
(b) (4) [redacted]	(b) (4) [redacted]	(b) (4) [redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 0910-0120
Expiration Date: December 31, 2013
See OMB Statement on page 5.

Date of Submission	User Fee Payment ID Number	FDA Submission Document Number *(if known)*
10/09/2012	(b) (4)	

SECTION A TYPE OF SUBMISSION

PMA	PMA & HDE Supplement	PDP	510(k)	Meeting
☐ Original Submission	☐ Regular (180 day)	☐ Original PDP	☒ Original Submission:	☐ Pre-510(K) Meeting
☐ Premarket Report	☐ Special	☐ Notice of Completion	☒ Traditional	☐ Pre-IDE Meeting
☐ Modular Submission	☐ Panel Track (PMA Only)	☐ Amendment to PDP	☐ Special	☐ Pre-PMA Meeting
☐ Amendment	☐ 30-day Supplement		☐ Abbreviated (Complete section I, Page 5)	☐ Pre-PDP Meeting
☐ Report	☐ 30-day Notice		☐ Additional Information	☐ Day 100 Meeting
☐ Report Amendment	☐ 135-day Supplement		☐ Third Party	☐ Agreement Meeting
☐ Licensing Agreement	☐ Real-time Review			☐ Determination Meeting
	☐ Amendment to PMA & HDE Supplement			☐ Other *(specify):*
	☐ Other			

IDE	Humanitarian Device Exemption (HDE)	Class II Exemption Petition	Evaluation of Automatic Class III Designation (De Novo)	Other Submission
☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ Original Submission	☐ 513(g)
☐ Amendment	☐ Amendment	☐ Additional Information	☐ Additional Information	☐ Other *(describe submission):*
☐ *Supplement*	☐ *Supplement*			
	☐ Report			
	☐ Report Amendment			

Have you used or cited Standards in your submission? ☐ Yes ☐ No *(If Yes, please complete Section I, Page 5)*

SECTION B SUBMITTER, APPLICANT OR SPONSOR

Company / Institution Name	Establishment Registration Number *(if known)*		
Forward Science LLC			
Division Name *(if applicable)*	Phone Number *(including area code)*		
	855-696-7254		
Street Address	FAX Number *(including area code)*		
2511 Wind Fall Ln	855-329-6725		
City	State / Province	ZIP/Postal Code	Country
Sugar Land	Texas	77479	USA
Contact Name			
Brian Pikkula			
Contact Title	Contact E-mail Address		
President & CTO	bpikkula@oralid.com		

SECTION C APPLICATION CORRESPONDENT (e.g., consultant, if different from above)

Company / Institution Name			
Division Name *(if applicable)*	Phone Number *(including area code)*		
Street Address	FAX Number *(including area code)*		
City	State / Province	ZIP Code	Country
Contact Name			
Contact Title	Contact E-mail Address		

PSC Publishing Services (301) 443-6740 EF

SECTION D1 REASON FOR APPLICATION - PMA, PDP, OR HDE

- ☐ New Device
- ☐ Withdrawal
- ☐ Additional or Expanded Indications
- ☐ Request for Extension
- ☐ Post-approval Study Protocol
- ☐ Request for Applicant Hold
- ☐ Request for Removal of Applicant Hold
- ☐ Request to Remove or Add Manufacturing Site

- ☐ Process change:
  - ☐ Manufacturing ☐ Packaging
  - ☐ Sterilization
  - ☐ Other *(specify below)*

- ☐ Response to FDA correspondence:

- ☐ Change in design, component, or specification:
  - ☐ Software / Hardware
  - ☐ Color Additive
  - ☐ Material
  - ☐ Specifications
  - ☐ Other *(specify below)*

- ☐ Labeling change:
  - ☐ Indications
  - ☐ Instructions
  - ☐ Performance Characteristics
  - ☐ Shelf Life
  - ☐ Trade Name
  - ☐ Other *(specify below)*

- ☐ Location change:
  - ☐ Manufacturer
  - ☐ Sterilizer
  - ☐ Packager

- ☐ Report Submission:
  - ☐ Annual or Periodic
  - ☐ Post-approval Study
  - ☐ Adverse Reaction
  - ☐ Device Defect
  - ☐ Amendment

- ☐ Change in Ownership
- ☐ Change in Correspondent
- ☐ Change of Applicant Address

- ☐ Other Reason *(specify)*:

SECTION D2 REASON FOR APPLICATION - IDE

- ☐ New Device
- ☐ New *Indication*
- ☐ Addition of Institution
- ☐ Expansion / Extension of Study
- ☐ IRB Certification
- ☐ Termination of Study
- ☐ Withdrawal of Application
- ☐ Unanticipated Adverse Effect
- ☐ Notification of Emergency Use
- ☐ Compassionate Use Request
- ☐ Treatment IDE
- ☐ Continued Access

- ☐ Change in:
  - ☐ Correspondent / Applicant
  - ☐ Design / Device
  - ☐ Informed Consent
  - ☐ Manufacturer
  - ☐ Manufacturing Process
  - ☐ Protocol - Feasibility
  - ☐ Protocol - Other
  - ☐ Sponsor

- ☐ Report submission:
  - ☐ Current Investigator
  - ☐ Annual Progress Report
  - ☐ Site Waiver Report
  - ☐ Final

- ☐ Response to FDA Letter Concerning:
  - ☐ Conditional Approval
  - ☐ Deemed Approved
  - ☐ Deficient Final Report
  - ☐ Deficient Progress Report
  - ☐ Deficient Investigator Report
  - ☐ Disapproval
  - ☐ Request Extension of Time to Respond to FDA
  - ☐ Request Meeting
  - ☐ Request Hearing

- ☐ Other Reason *(specify)*:

SECTION D3 REASON FOR SUBMISSION - 510(k)

- ☒ New Device
- ☐ Additional or Expanded Indications
- ☐ Change in Technology

- ☐ Other Reason *(specify)*:

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

1	NXV	2		3		4	
5		6		7		8	

Summary of, or statement concerning, safety and effectiveness information

- [x] 510 (k) summary attached
- [ ] 510 (k) statement

Information on devices to which substantial equivalence is claimed *(if known)*

	510(k) Number		*Trade or Proprietary or Model Name*		*Manufacturer*
1	K102083	1	VELscope Vx	1	LED Dental, Inc.
2	K101140	2	Dentlight Oral Exam Light Kit	2	DentLight, Inc.
3		3		3	
4		4		4	
5		5		5	
6		6		6	

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification name

Oral Examination Light

	Trade or Proprietary or Model Name for This Device		Model Number
1	OralID	1	
2		2	
3		3	
4		4	
5		5	

FDA document numbers of all prior related submissions *(regardless of outcome)*

1	2	3	4	5	6
7	8	9	10	11	12

Data Included in Submission

- [ ] Laboratory Testing
- [ ] Animal Trials
- [ ] Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code	C.F.R. Section *(if applicable)*	Device Class
NXV	872.6350	[ ] Class I [x] Class II
Classification Panel: Dental		[ ] Class III [ ] Unclassified

Indications *(from labeling)*

OralID is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia. OralID excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence. OralID is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion to aid in determining the appropriate margin for surgical excision. OralID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the OralID™ blue light.

Note: Submission of the information entered in Section H does not affect the need to submit device establishment registration.	FDA Document Number *(if known)*

SECTION H — MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION

☒ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☒ Manufacturer ☐ Contract Manufacturer	☐ Contract Sterilizer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Forward Science LLC	
Division Name *(if applicable)*	Phone Number *(including area code)*
	855-696-7254
Street Address	FAX Number *(including area code)*
2511 Wind Fall Ln	855-329-6725

City	State / Province	ZIP Code	Country
Sugar Land	Texas	77479	USA

Contact Name	Contact Title	Contact E-mail Address
Brian Pikkula	President & CTO	bpikkula@oralid.com

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Manufacturer	☐ Contract Sterilizer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Division Name *(if applicable)*	Phone Number *(including area code)*
Street Address	FAX Number *(including area code)*

City	State / Province	ZIP Code	Country

Contact Name	Contact Title	Contact E-mail Address

☐ Original ☐ Add ☐ Delete	Facility Establishment Identifier (FEI) Number	☐ Manufacturer ☐ Contract Manufacturer	☐ Contract Sterilizer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number
Division Name *(if applicable)*	Phone Number *(including area code)*
Street Address	FAX Number *(including area code)*

City	State / Province	ZIP Code	Country

Contact Name	Contact Title	Contact E-mail Address

SECTION I — UTILIZATION OF STANDARDS

Note: Complete this section if your application or submission cites standards or includes a *"Declaration of Conformity to a Recognized Standard"* statement.

	Standards No.	Standards Organization	Standards Title	Version	Date
1	13485	ISO	Medical devices -- Quality management systems -- Requirements for regulatory purposes	2003	10/09/2012
2	14971	ISO	Medical devices -- Application of risk management to medical devices	2007	10/09/2012
3					
4					
5					
6					
7					

Please include any additional standards to be cited on a separate page.

Public reporting burden for this collection of information is estimated to average 0.5 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Table of Contents

K123169

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

October 04, 2012

K 28

RE: Traditional "510(k) Notification" (21 CFR 807.90(e))

To whom it may concern:

This submission is being made in compliance with Section 510(k) of the Food, Drug, and Cosmetic Act as amended by the Medical Device Amendments of 1976, the Safe Medical Devices Act of 1990, and the Food and Drug Administration Modernization Act of 1997, and the Office of Compliance, Center for Devices and Radiological Health Guidance Document on the Premarket Notification 510(k): Regulatory Requirements for Medical Devices.

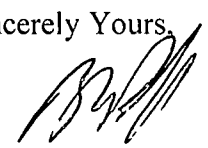
The purpose of this submission is to notify FDA, in compliance with Section 510(k) of the Food, Drug, and Cosmetic Act, Forward Science LLC's intent to introduce, a new product, OralID™, an Oral Examination Light and accessories, into commercial distribution.

OralID™ is a Class II device under Regulation Number 21 CFR § 872.6350, UltraViolet Detector, product code NXV. OralID™ accessories include Photosensitive glasses (21 CFR §886.5850, HQY) which are class I (Exempt).

An original, two hard copies and one electronic (pdf) copy of this Premarket Notification are being submitted in accordance with 21 CFR 807.90(e). Confidentially is requested per 21 CFR 807.95

If you have any questions regarding this submission, please contact Brian Pikkula by phone at 855-696-7254 or by email at bpikkula@oralID.com.

Sincerely Yours,



Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

III. GENERAL INFORMATION

A. 510(k) Application

OralID™ and Accessories

B. Application Date

October 04, 2012

C. Submitter's Name and Address

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

D. Contact Person

Brian Pikkula, PhD
President & CTO

E. Trade / Device Name

Proprietary Name: OralID™
Common Name: Oral Examination Light and accessories

F. Establishment Registration Number of Submitter

Pending Registration

G. Device Classification

Regulation Number:	21 CFR § 872.6350
Panel:	Dental
Classification Name:	UltraViolet Detector
Regulatory Class:	II
Product Code:	NXV (EAQ)
Regulation Number:	21 CFR § 886.5850
Panel:	Ophthalmic
Classification Name:	Photosensitive glasses
Regulatory Class:	I (Exempt)
Product Code:	HQY

H. Reason for 510(k) Submission

The purpose of this submission is to notify FDA, in compliance with Section 510(k) of the Food, Drug, and Cosmetic Act, Forward Science LLC's intent to introduce a new product, OralID™, an Oral Examination Light and accessories, into commercial distribution.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Predicate Device(s)

DentLight Oral Exam Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

Action Taken to Comply with Section 514 of the Act

Performance Standards have not been established.

I. Design and Use of the Device

Question	YES	NO
Is the device intended for prescription use (21 CFR 801 Subpart D)?[A]	X	
Is the device intended for over-the-counter use (21 CFR 807 Subpart C)?[A]		X
Does the device contain components derived from a tissue or other biologic source?		X
Is the device provided sterile?		X
Is the device intended for single use?		X
Is the device a reprocessed single use device?		X
If yes, does this device type require reprocessed validation data?		X
Does the device contain a drug?		X
Does the device contain a biologic?		X
Does the device use software?		X
Does the submission include clinical information?		X
Is the device implanted?		X

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): _____

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

OralID™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence.

(b) (4) [redacted]

OralID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the OralID™ blue light.

Prescription Use_____X_____ (Per 21 CFR 801 Subpart D) AND/OR Over-the-Counter_____ (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

V. 510(k) SUMMARY

Submitted by:

Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

Contact Person: Brian Pikkula, PhD

Date Prepared: October 04, 2012

Proprietary Name: OralID™

Common Name: Oral Examination Light and Accessories

Classification:

Class II:	21 CFR § 872.6350
Class I: (Exempt)	21 CFR § 886.5850

Classification Name: Ultra-violet Detector – NXV (EAQ)
Photosensitive glasses – HQY (Exempt)

Predicate Devices:

DentLight Oral Exan Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

Device Description:

OralID™ is a battery operated (CR123A), hand-held, oral illumination and examination light designed for use by dental and medical professionals to be used as an adjunctive tool for fluorescence visualization of oral mucosal tissue. OralID™ accessories include two pair of filtered eyewear.

Intended Use:

OralID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

OralID™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence.

(b) (4) [redacted]

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

OralID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the OralID™ blue light. OralID™ eyewear has been designed to allow transmission of light (b) (4)

Technological Characteristics:

OralID™ uses "CR123A" batteries to operate one or more high intensity LEDs to emit a safe, visible blue light to enhance the identification and visualization of oral mucosal abnormities that may not be apparent or visible to the naked eye. While using the filtered glasses, OralID™ oral examination light shows healthy tissue in fluorescence green while abnormal tissue appears dark due to lack of fluorescence.

The direct visualization of fluorescent tissues is using the body's natural system to identify suspicious tissue quickly that may require further investigation. The loss of natural tissue fluorescence can help identify subclinical high-risk fields with cancerous and precancerous changes **Clinical Cancer Research Vol. 12, 6716-6722, November 15, 2006.**

Substantial Equivalence

OralID™ has the same intended use and technical characteristics as the predicate devices (K101140 and K102083); each uses fluorescence as the primary mode for enhanced visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces a violet light and views fluorescence through filtered loupes.

Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens.

OralID™ uses "CR123A" batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk of the recharging process.

The operational principles of the proposed and predicate devices are identical with the primary mode for enhanced visualization of tissue through fluorescence. Each of these devices is powered by batteries and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

VI. Truthful and Accurate Statement

TRUTHFUL AND ACCURATE STATEMENT

I certify, in my capacity as President and Chief Technical Officer of Forward Science LLC, that I believe to the best of my knowledge, that all data and information submitted in this 510(k) Premarket Notification Submission is truthful and accurate and that no material fact has been omitted.

October 04, 2012
Date

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77478
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

VII. Class III Summary and Certification

Not Applicable

VIII. Financial Certification or Disclosure Statement

Not Applicable

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IX. Declaration of Conformity

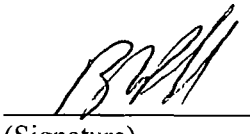
US Declaration of Conformity

Application of Directive(s)	U.S. Title 21 CFR, part 800
Standards to which Conformity is Declared	ISO 13485 (Quality Standards) ISO 14971 (Risk Management)
Manufacturer's Name and Address	Forward Science LLC 2511 Wind Fall Ln Sugar Land, TX 77479 Ph: 855-696-7254 Fax: 855-329-6725
Authorized Representative and Representative's Address	Brian Pikkula, PhD 2511 Wind Fall Ln Sugar Land, TX 77479 Ph: 855-696-7254 Fax: 855-329-6725
Type of Device	Oral Examination Light and accessories
Model Number	ORALID™
Classification	Class II
Year of Manufacture	2012-2013

I the undersigned hereby declare that the equipment specified above conforms to the above stated Directive(s) and Standard(s).

Place: Sugar Land, Texas USA

Date: October 04, 2012



(Signature)

Brian Pikkula, Ph.D.
(Name)

President & CTO
(Position)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

X. Executive Summary

Device Description:

OralID™ is a battery operated (CR123A), hand-held, oral illumination and examination light designed for use by dental and medical professionals to be used as an adjunctive tool for fluorescence visualization of oral mucosal tissue. OralID™ accessories include user and patient glasses.

Intended Use:

OralID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

OralID™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence.

(b) (4) [redacted]

OralID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the OralID™ blue light. OralID™ eyewear has been designed to allow transmission of light (b) (4) .

Technological Characteristics:

OralID™ uses "CR123A" batteries to operate one or more high intensity LEDs to emit a safe, visible blue light to enhance the identification and visualization of oral mucosal abnormities that may not be apparent or visible to the naked eye. While using the filtered glasses, OralID™ oral examination shows healthy tissue in a fluorescence green while abnormal tissue appears dark due to lack of fluorescence.

The direct visualization of fluorescent tissues is using the body's natural system to identify suspicious tissue quickly that may require further investigation. The loss of natural tissue fluorescence can help identify subclinical high-risk fields with cancerous and precancerous changes **Clinical Cancer Research Vol. 12, 6716-6722, November 15, 2006.**

Substantial Equivalence

OralID™ has the same intended use and technical characteristics as the cleared predicate devices (K101140 and K102083); each uses fluorescence as the primary mode for enhanced visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces a violet light and views fluorescence through filtered loupes. Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens. OralID™ uses primary batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk associated with for the recharging station. The operational principles of the proposed and predicate devices are identical with the primary mode for enhanced visualization of tissue through fluorescence. Each of these devices is powered by a battery power source, and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

Comparison Parameters	ORALID™	VELscope (K102083)	DentLight (K101140)
Intended Use;	Identification and visualization of oral mucosal abnormalities, such as oral cancer or premalignant dysplasia.	SE	SE
Intended Use;	Direct visualization of the resulting natural tissue fluorescence.	SE	SE
Intended Use;	(b) (4)	(b) (4)	
Lens Filter		SE	SE
Materials		SE	SE
Energy Used/Delivered		SE	SE
Light Emission Blue		SE	NO
Light intensity		SE	SE
Power/Voltage/Type	2x CR123A Batteries (6.0V)	SE	SE
Protection from shock	(b) (4)	SE	SE
Environmental operation and storage temperature:	32 - 104°F (0 - 40° C)	SE	SE
Target Population	All	SE	SE
Where Used	Clinical, OR, & ICU	SE	SE
Incompatibility: Device / Environment	None Known	SE	SE
Mechanical Safety	YES	SE	SE
Chemical Safety	N/A	N/A	N/A
Electrical Safety	IEC 60601 (collateral standards EMC/EMI)	SE	SE
Radiation Safety - Threshold Limit Values	(b) (4)	SE	SE
Product Standards Met	N/A	N/A	N/A
Sterilization	N/A	N/A	N/A
Human Factors	YES	SE	SE
Product Labeling	Primary Package and Operations manual	SE	SE
Other Features	Physician & Patient Photosensitive Glasses	SE	SE

Performance Testing and Compliance:

The following testing was conducted to evaluate the functionality and performance of the proposed OralID™:

(b) (4)

The performance data provided and the similarities between OralID™ and the predicate devices support the safety and effectiveness of OralID™ for the indications for use.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

XI. Device Description and Specifications

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

OralID™ Specifications

Feature / Component	Specification
Light	
LED	(b) (4)
Radiant flux	
Projected light image	
Peak Wavelength	
Safety	
Threshold Limit Value	(b) (4)
Cross contamination	
Electrical	
Power source	2x primary CR123A batteries
Main Body	
Material	(b) (4)
Dimensions	< 175 mm length and < 30 mm diameter
Labeling	
Printed	Primary label on box and Operator's Manual
On device	Serial number and OralID logo on device.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

(b) (4)

[redacted]

The OralID™ was designed, manufactured, tested and released under the USFDA's QSR and the ISO 13485 requirements to comply with stated standards. The ORALID® is manufactured by:

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

(b) (4)

[redacted]

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

XII. Substantial Equivalence

The OralID™ is used for the same purpose as the predicate devices. The design, materials, method of operation, and labeling are substantially equivalent.

Each device is to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities by exciting the tissue with light and allowing the direct visualization of the resulting natural tissue fluorescence. OralID™ has the same intended use and technical characteristics as the cleared predicate devices (K101140 and K102083); each uses fluorescence as the primary mode for enhanced visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces violet light and views fluorescence through filtered loupes. Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens. OralID™ uses primary batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk associated with for the recharging station. The operational principles of the proposed and predicate devices are identical with the primary mode for enhanced visualization of tissue through fluorescence. Each of these devices is powered by a battery power source, and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Comparison Matrix

Comparison Parameters	ORALID™	VELscope (K102083)	DentLite (K101140)
Intended Use;	Identification and visualization of oral mucosal abnormalities, such as oral cancer or premalignant dysplasia.	SE	SE
Intended Use;	Direct visualization of the resulting natural tissue fluorescence.	SE	SE
Intended Use;	(b) (4)	(b) (4)	
Lens Filter		SE	SE
Materials		SE	SE
Energy Used/Delivered		SE	SE
Light Emission Blue		SE	NO
Light intensity		SE	SE
Power/Voltage/Type	2x CR123A Batteries (6.0 v)	SE	SE
Protection from shock	(b) (4)	SE	SE
Environmental operation and storage temperature:	32 - 104°F (0 - 40° C)	SE	SE
Target Population	All	SE	SE
Where Used	Clinical, OR, & ICU	SE	SE
Incompatibility: Device / Environment	None Known	SE	SE
Mechanical Safety	YES	SE	SE
Chemical Safety	N/A	N/A	N/A
Electrical Safety	IEC 60601 (collateral standards EMC/EMI)	SE	SE
Thermal Safety	YES	SE	SE
Radiation Safety - Threshold Limit Values	(b) (4)	SE	SE
Product Standards Met	N/A	N/A	N/A
Sterilization	N/A	N/A	N/A
Human Factors	YES	SE	SE
Product Labeling	Primary Package and Operations manual	SE	SE
Other Features	Physician & Patient Photosensitive Glasses	SE	SE

The OralID™ is substantially equivalent to:

DentLight Oral Exan Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

510(k) summary and product literature are found in Attachment B.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

XIII. Proposed Labeling

(b) (4)

[redacted]

XIV. Sterilization and Shelf Life

(b) (4)

[redacted]

XV. Biocompatibility

(b) (4)

[redacted]

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

XVI. Software

- Not Applicable

XVII. Electrical Safety

The OralID™ meets electrical safety requirements under IEC 60601 and collateral standards (as applicable).

XVIII. Performance Testing – Bench

The following testing was conducted to evaluate the functionality and performance of the proposed OralID™:

(b) (4) [redacted]

The OralID™ was evaluated for performance measurement and meets or exceeds its approved specifications for materials, energy delivered, light intensity, and electrical, thermal, and mechanical safety.

The performance data provided and the similarities between OralID™ and the predicate devices support the safety and effectiveness of OralID™ for the indications for use.

XIX. Performance Testing – Animal

- Not Applicable

XX. Performance Testing – Clinical

OralID™ is effective in enhancing the visualization of:

(b) (4) [redacted]

Attachment C includes numerous scientific abstracts and studies providing evidence to support the use of light for the visualization of natural tissue fluorescence.

[redacted]

VOLUME II

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Volume II Section XXI	Title Attachments	Page Number
A	OralID™ Proposed Package Labeling	2
A1	Primary Label	2
A2	Glasses Label	2
A3	Instructions For Use	3
B	Predicate 510(k)'s and Product Literature	5
B1	LED Medical Diagnostics – VELscope Vx (K102083)	5
B2	LED Marketing Materials	10
B3	LED Clinical Data (432 nm green fluorescence)	21
B4	DentLight Oral Exam Light Kit (K101140)	42
B5	DentLight Marking Materials	48
C	Abstracts supporting Indications for Use and Marketing Claims and Bibliography	52

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

A1. ORALID™ Examination Light Set

(b) (4)

A2. Glasses Labels (2)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

A3. Instructions For Use (IFU) Package Insert

OralID
See what you've been missing.

INSTRUCTIONS FOR USE

DEVICE DESCRIPTION

OralID™ is a battery operated, hand-held oral examination light to be used as an adjunctive device for oral mucosal screening. Accessories include filtered eyewear for both the clinician and patient.

OralID™ emits a safe, visible blue light into the oral cavity. The OralID™ eyewear is worn by the healthcare professional to enhance the visual effects of the blue light during the examination. Normal, healthy tissue fluoresces green while abnormal tissue appears dark due to lack of fluorescence.

FLUORESENCE TECHNOLOGY

Traditional oral examinations include tactile and visual methods, utilizing reflected light to visualize the oral cavity. OralID™ utilizes fluorescence technology to examine the oral cavity, being able to identify tissue changes in some cases before they become visible to the naked eye.

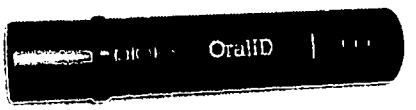
INTENDED USE

OralID™ is intended to be used by qualified health-care providers to enhance the visualization and identification of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as dysplasia and/or oral cancer.

(b) (4)

PACKAGE CONTENTS

- OralID™ Device
- Clinical Filtered Glasses
- Patient Safety Glasses
- 4 CR123A lithium batteries
- IFU (Instructions for use)
- Storage/Display Box



DEVICE REGISTRATION

Please register your OralID™ device online at www.oralid.com/register . Registration will expedite the warranty process of the device and to help keep you informed of the most recent news regarding oral screening.

WARRANTY

Forward Science LLC warrants this equipment to the original purchaser against any manufacturing defects for a period of one (1) year from the original date of purchase. Warranty registration of your OralID device at www.oralid.com/register will expedite the warranty process.

The warranty is void if product is not used and maintained according to the User Manual provided with the device.

Should service repair be required, please contact OralID™ Customer Support to obtain instructions and return material authorization (RMA) number. The original purchaser is responsible for shipping and handling charges when returning product for servicing.

- Due to the high power LED, this device may be warm to the touch after several minutes of illumination. This is normal.
- Do not look directly into the light.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

INITIAL SET UP

Insert batteries per instructions

THE ORALID EXAMINATION

Before any oral examination occurs, please review all of the patient's medical and dental history.

1. Conduct a thorough visual and manual oral examination, both extra-oral and intra-oral per the ADA guidelines.
2. The filtered eyewear should be placed on at this time for both the clinician and patient.
3. If possible, dim the lights in the operatory (not necessary for use).
4. Press the ON/OFF power button at the back of the device (Figure X).
5. Using the OralID™ device, repeat the intra-oral examination
   - Normal tissue emits a green fluorescence
   - Abnormal tissue appears dark due to lack of fluorescence

   Note: Inflammation typically appears dark due to increased blood vessels.
6. Document all relevant findings. (Documentation forms can be found at www.oralid.com)
7. Inform the patient of any/all relevant findings and appropriate course of action.
8. Follow up in 2 weeks or refer as appropriate.

Remember: The Gold Standard for diagnosing abnormal lesions is a surgical biopsy.

CONTACT INFORMATION

Phone: 855.MY ORALID (855.696.7254)
Fax: 855.FAX ORALID (855.329.6725)
Web: www.oralid.com
Email: info@oralid.com

- Do not charge batteries (when drained please dispose of them per your local laws or regulations).
- Do not mix old and new batteries (use batteries in pairs).
- Do not mix different brand batteries.
- Only use high quality,name brand, U.S Manufactured CR123A batteries.

MAINTENENCE

OralID™ Device should be stored in a cool, dry place. OralID™ should be cleaned and disinfected between each patient use. The external surfaces of the Handpiece should then be wiped down with a hospital-grade surface disinfectant and a towelette or gauze, e.g. Caviwipes™ or equivalent. Do not use disinfectants with alcohol content over 70%.

Filtered Eyewear (Clinician and Patient)

Filtered eyewear should be cleaned with soap and water. Do not use alcohol or alcohol-based products, as this will degrade the lenses.

(b) (4)

(b) (4)

MANUFACTURER INFORMATION

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479

OralID™ Patent Pending

U.S. Federal law restricts this device to sale by or on the order of a Dentist, Physician, or other appropriately licensed health-care professional.

FS-10 Rev1.0

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

B1. LED DENTAL INC Predicate 510(k)'s

K102083

510(k) Summary

NOV 18 2010

Submitter's Name: David Morgan, PhD

Date of Submission: July 23 2010

Address: 235 - 5589 Byrne Road
Burnaby, BC
V5J 3J1
Canada

Contact Person: David Morgan, PhD

Phone: (604) 434-4614, ext. 262

E-mail: david.morgan@leddental.com

Fax: (604) 434-4612

Device Name: VELscope Vx

Common Name: Oral Examination Light

Classification Name: Ultraviolet detector

Marketed Device of Equivalence: VELscope (K070523)

Description of Device:

The VELscope Vx system is a natural tissue fluorescence direct visualization system to be used as an adjunctive tool for oral mucosal examination.

The main components of VELscope are the Handpiece, incorporating light source, viewing optics and rechargeable battery, Charging Cradle and external power supply. The VELscope Handpiece emits a safe, visible, blue light into the oral cavity, which excites the oral tissue and causes it to fluoresce. The oral cavity can then be examined in real time and suspicious tissue that may require further investigation can be quickly identified. When viewed through the VELscope Handpiece, abnormal tissue typically appears as an irregular, dark area that stands out against the otherwise normal green fluorescence pattern of surrounding health tissue.

Intended Use:

VELscope Vx is intended to be used by a dentist or health-care provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

VELscope Vx is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Characteristics of VELscope compared to Predicate Device:

As compared to the predicate device, the VELscope Vx system has identical Indications for Use.

The main technological differences between the VELscope Vx and the predicate VELscope system are:

- The light source has now been integrated into the Handpiece by replacing the metal halide lamp originally situated in a separate Light Source Unit with a ring of blue light emitting diodes (LED's) now situated around the distal window of the Handpiece itself.
- The VELscope Vx Handpiece can now operate in a completely cordless fashion powered by a rechargeable lithium ion battery.

The essential performance specifications of the device are equivalent to the predicate VELscope device:

- (b) (4)) is the same as the predicate device and the optical output power in that excitation band is comparable.
- The emission (viewing) optics are identical to the predicate device.

Non-Clinical Data

Spectral data comparing the optical intensity distribution of the VELscope Vx excitation light with that of the predicate VELscope are provided to support substantial equivalence.

Clinical Data

Clinical photographs were taken of a variety of oral mucosal lesions from patients referred to oral medicine and oral dysplasia clinics. Conventional (white light) as well as fluorescence photographs using both the predicate VELscope and the VELscope Vx were acquired. No adverse events or complications were reported. A comparison of the predicate VELscope and VELscope Vx images supports the substantial equivalence of the VELscope Vx with the predicate VELscope.

Conclusion

The VELscope Vx system has identical indications for use as the predicate VELscope system and comparative excitation spectral data and clinical fluorescence photographs of oral mucosal lesions support the fact that, despite the technological differences, the VELscope Vx system is substantially equivalent to the VELscope system already cleared under 510(k) – K070523.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room -WO66-G609
Silver Spring, MD 20993-0002

David Morgan, PhD
Chief Science Officer
LED Dental Incorporated
235-5589 Byrne Road
Burnaby, BC
Canada V5J 3J1

NOV 18 2010

Re: K102083
Trade/Device Name: VELscope Vx
Regulation Number: 21 CFR 872.6350
Regulation Name: Ultraviolet Detector
Regulatory Class: II
Product Code: NXV
Dated: October 18, 2010
Received: October 29, 2010

Dear Dr. Morgan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

for

Anthony D. Watson, B.S., M.S., M.B.A.
Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Indications for Use

510(k) Number (if known): K102083

NOV 18 2010

Device Name: VELscope Vx

Indications For Use:

VELscope Vx is intended to be used by a dentist or health-care provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

VELscope Vx is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision.

Prescription Use ___X___ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Susan Runner

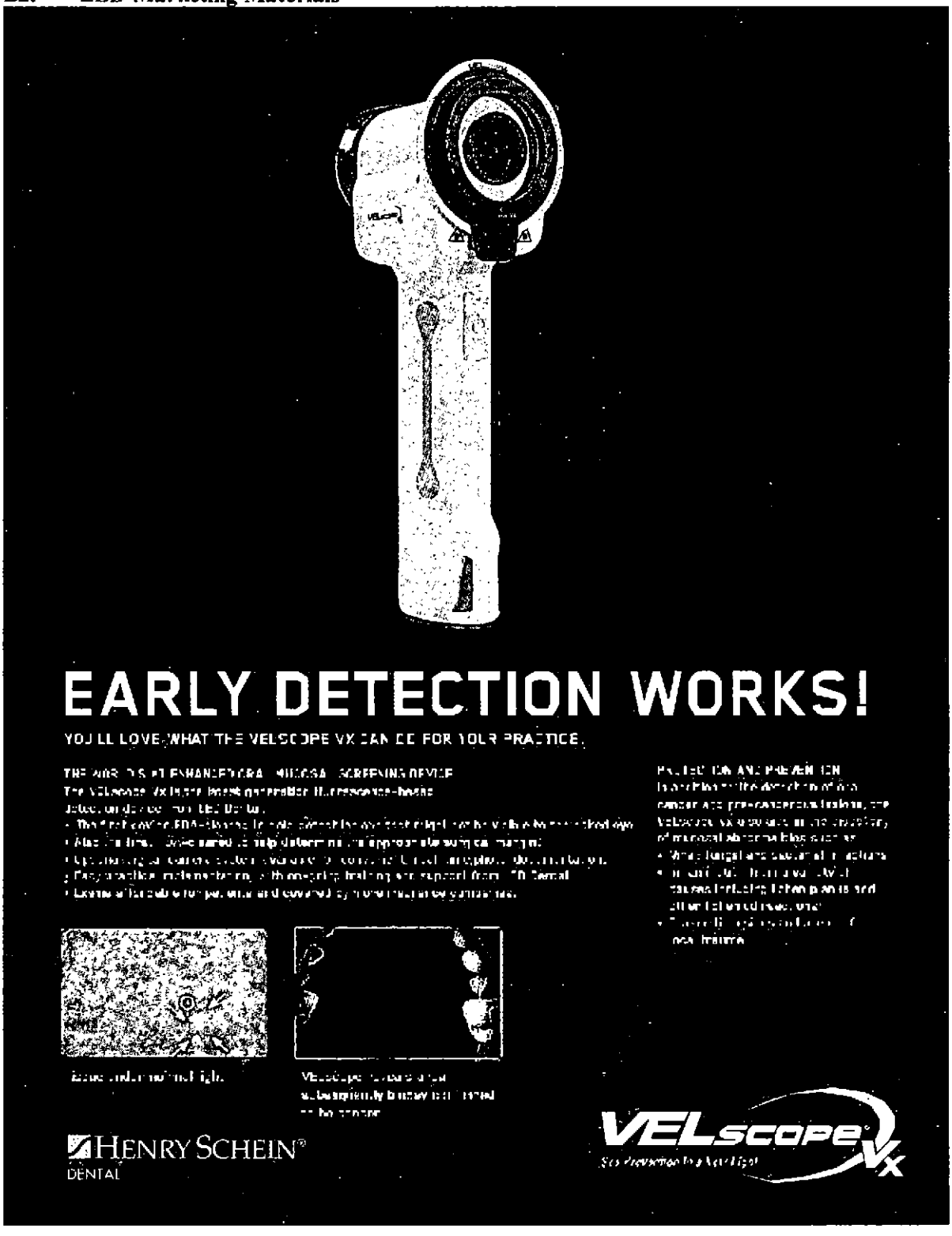
(Division Sign-Off)
Division of Anesthesiology, General Hospital
Infection Control, Dental Devices

510(k) Number: _____ Page 1 of ___1___

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

B2. LED Marketing Materials



FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

VELscope Vx

- Helps detect changes unseen with the naked eye
- No messy dye or unpleasant rinses
- Cordless, portable and rechargeable
- Exam takes only 2 minutes
- Large illumination area for faster, more effective exam
- High power facilitates use in all lighting conditions
- As seen on the nationally syndicated The Dr. Oz Show

Establish Your Own Standard of Excellence

The difference between early and late detection of oral cancer can be the difference between life and death.

- Oral cancer is most often discovered in late stages, when the 5-year survival rate is only around 30%.
- When discovered early, however, the survival rate leaps to about 82%.

Your 2-minute VELscope Vx exam can turn a routine visit to your practice into a life-saving experience.

Clinically Proven

A recent University of Washington study of 620 low-risk patients showed how the VELscope helped detect all 28 lesions-including 5 cases of dysplasia-that were missed by the naked eye.*

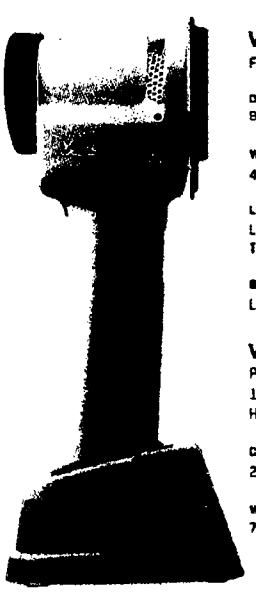
Share Your Vision--Conveniently!

The optional digital camera attachment system for the VELscope Vx enables you to quickly and easily take high quality fluorescence and white light pictures as photo-documentation for your records and to facilitate communication with specialists to whom you might refer patients.

Powered by a 12-megapixel Canon® digital camera, the system includes a Vx adapter, memory card, battery pack and charger, AV cable and wrist strap. With a simple twist-on connection to the VELscope Vx handpiece,it's an ultra-convenient add-on that no practice should be without.

* Edmond L. Truelove et al, General Dentistry, July/August 2011, 281-289.

VELscope Vx (791-0012) **$2,749.99**



VELSCOPE VX
FLUORESCENCE VISUALIZATION HANDPIECE

DIMENSIONS
8.9" H X 2.2" W X 3.4" D

WEIGHT
413 G (14.6 OZ.) P

LED LIGHT SOURCE
LIFE EXPECTANCY IS EQUIVALENT TO THE LIFE OF THE DEVICE.

BATTERY TYPE
LITHIUM ION

VX CHARGING CRADLE
POWER SUPPLY: 100-240V, 50-60HZ. 1.5A OUTPUTS 12V, 5A. UTILIZES A HOSPITAL-GRADE POWER CORD.

DIMENSIONS
2.5" H X 4" W X 4" D

WEIGHT
760 G (27.04 OZ.)

Vx Camera System (791-0018) **$499.99**

CONTAINS ONE CAMERA, ONE USB CABLE, ONE AV CABLE, ONE ADAPTER, ONE MEMORY CARD DISK, ONE BATTERY PACK, ONE BATTERY CHARGER, ONE WRIST STRAP, ONE QUICK START GUIDE, ONE CD AND ONE INSTRUCTION BOOKLET.

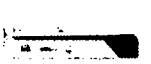
Vx Disposable Starter Kit (791-0015) **$399.99**

CONTAINS TWO 128-COUNT BOXES OF VELCAPS PLUSONE 250-COUNT BOX OF VELSHEATHS ($499.97 VALUED

VELcap Vx (791-0013) **$229.99**

DISPOSABLE PROTECTIVE, ASEPTIC, ANTI-FOG LENS COVERS ARE COMPACT, EASY AND MORE EFFICIENT TO STORE, AND QUICK TO ATTACH AND REMOVE AFTER EACH PATIENT. 128 PER BOX.

VELsheath Vx (791-0014) **$39.99**



DISPOSABLE HANDPIECE ASEPSIS BARRIERS. 250 PER BOX.

Like us on Facebook
facebook.com/velscope

twitter/velscope

YouTube
youtube.com/velscope

TO ORDER CALL: 1.800.372.4346 8am - 9pm (et) **FAX:** 1.800.732.7023 24 Hours
www.henryscheindental.com

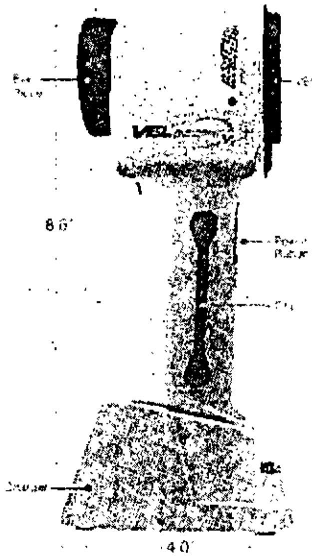
VELscope Vx
See Prevention in a New Light

LED Dental Inc. | www.velscope.com

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

The VELscope Vx



The VELscope Vx and charger

VELscope Vx

Fluorescence visualization technology hand piece

Dimensions
6.6"h x 2.2"w x 3.4"d

Weight
413 g (14.6 oz.)

LED Light Source
Life expectancy is equivalent to the life of the device

Battery Type
Lithium Ion

Vx Charging Cradle

Power supply: 100-240V 50-60Hz, 1.5A outputs 12V 5A; utilizes a hospital-grade power cord

Dimensions
2.5"h x 4"w x 4"d

Weight
760 g (27.04 oz.)

VELscope Vx System Price
(including charger) **$2,499**

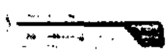
VELcap Vx

NOTE: A new VELcap Vx should be used with every patient.

Disposable protective, aseptic, anti-fog lens covers are compact, easy and more efficient to store, and quick to attach and remove after each patient.

Box of 128 units $230.40

VELsheath Vx



Disposable handpiece aseptic barriers

250 unit dispenser carton $39.95

Accessories

Dig for camera adapter

"Using a VELscope exam, I was able to visualize the oral source of the cancer. The surgeon removed it, and the patient is still with us over 6 years later. VELscope literally saved her life."

– Anthony Palombaro, DDS
Binghamton, NY

Comprehensive Training & Resources
LED Dental offers live & recorded training webinars – earn CE units online

- Clinical implementation protocols
- Visualization and interpretation
- Converting your patients into VELscope lovers

New & Improved Website: www.VELscope.com
A new, easy-to-use and informative site.

Increased Profitability
An affordable initial investment and low cost disposables mean you can charge as low as $15 or less per examination. Try our website ROI & Reimbursement Calculator and see how the VELscope Vx can add to your bottom line.

"I have found VELscope to be a very useful addition to the diagnostic methods used for the detection and management of oral dysplastic and malignant lesions.

There have been several occasions where its use allowed detection of malignant or dysplastic oral lesions when clinical suspicion of the lesion was very low or nonexistent.

The scope is easy to use and provides *a more objective method than visual inspection alone for determination of which* lesions demand immediate biopsy and more aggressive follow-up. Adding the VELscope to our diagnostic protocol has been extremely useful and resulted in detection of dangerous lesions that would have otherwise been undetected."

– Edmond L. Truelove, DMD, MSD
Chair & Professor Oral Medicine
School of Dentistry, University of Washington

VELscope Vx

For more information, or to order, please call (toll free)

888-541-4614 ext. 225

or visit us at **VELscope.com**

LED Dental, Inc. **Webinar Information** **Customer Support** **General Information**

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Meet the Light That's Making Headlines

VELscope Vx

Enhanced Oral Assessment

VELscope Vx!

- Cordless
- Compact
- Affordable - *even for multiple operatories!*
- Newest model release from LED Dental

The Right Light at the Right Price

- Provides the most powerful aid available for the discovery of oral abnormalities, including oral cancer
- Used regularly, allows practices to aspire to an advanced level of patient care
- Positions dental practices as pro-active and sophisticated

Set a Shining Example!

- Completely safe and painless
- Simple to use
- No unpleasant rinses or stains
- Entire exam in about two minutes

The VELscope can even play a role in *saving lives.*

LED Dental Inc.

Toll Fee NA: +1 888 541 4614 | Email: info@velscope.com
International +1 604 434 4614 | Website VELscope.com

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Single Out Suspicious Tissue...Early Discovery Can Save Lives

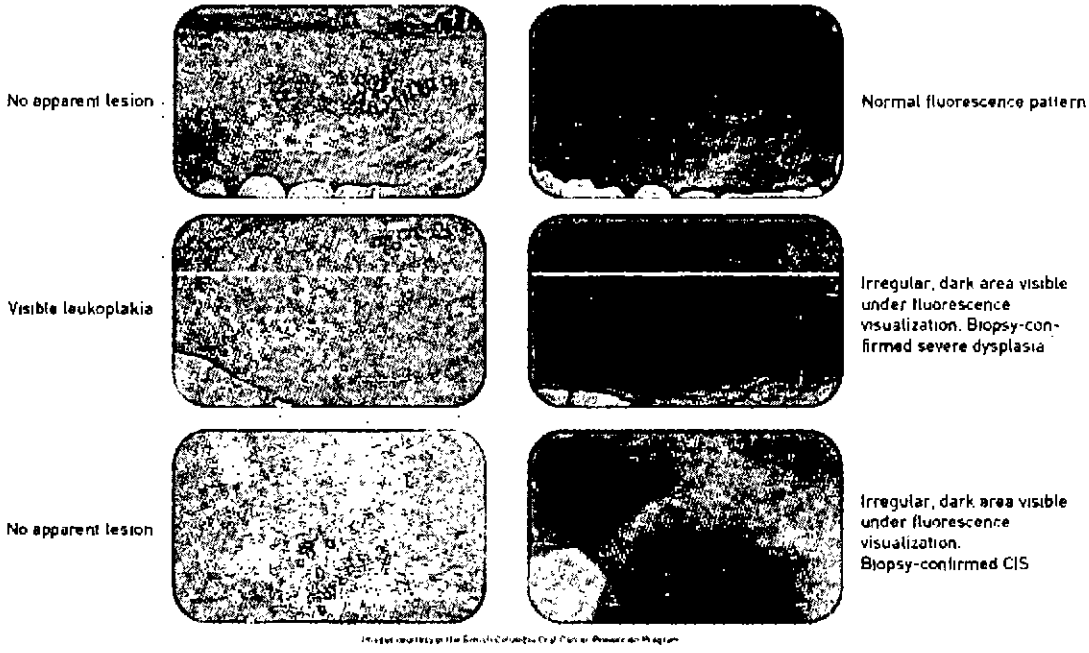
SYSTEM FEATURES:

- Painless, non-invasive, with no rinses or stains required
- An examination with the VELscope® System takes only one or two minutes and is easy to incorporate into your workflow
- Oral lesion mapping, tracking and patient management forms available online. Optional third-party photo-documentation solutions also available
- Flexible positioning: space-saving vertical or low profile horizontal orientation... your choice
- Disposable VELsheath/Barrier ensures asepsis
- Disposable anti-fog VELcap helps maintain asepsis and protects the Handpiece special filtering optics
- Convenient disposable VELtractor assists clinicians as a "third hand" during the examination and also serves as a measuring guide

VELSCOPE PROVIDES IMMEDIATE BENEFITS FOR THE PATIENT, CLINICIAN AND PRACTICE

The VELscope® System combines minimal per-patient costs with more effective screening. The investment for VELscope can be quickly recouped, yielding a substantial earning potential for the practice. Through the CDT code D0431*, an increasing number of insurance companies are recognizing VELscope as an adjunctive screening device

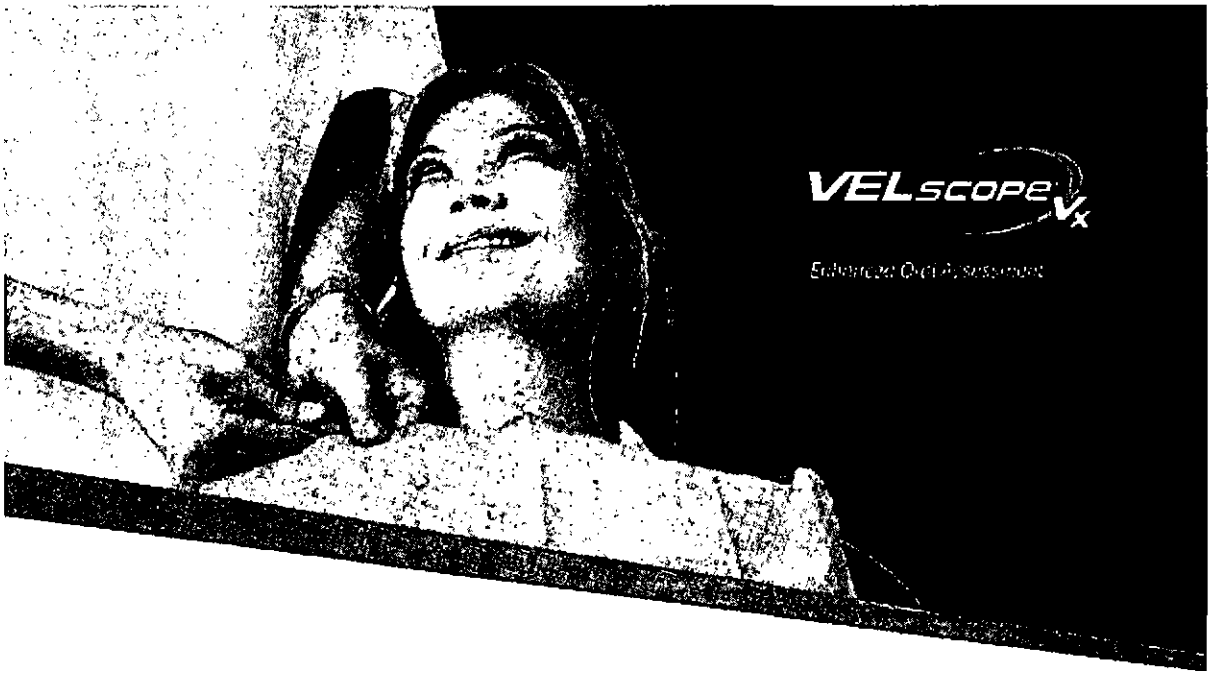
EXAMPLES OF DIRECT VISUALIZATION UNDER BOTH WHITE LIGHT AND VELSCOPE EXAMINATION



For further information about VELscope and LED Dental Inc., please visit our website at www.velscope.com.

LED Dental Inc.
201-15047 Marine Drive, White Rock, BC, Canada V4B 1C5
T +1 (888) 541-4614 Fax +1 (604) 541-4613 www.velscope.com

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254



VELscope Vx Step-By-Step Examination Guide

Note: This is an abbreviated clinical guide. Please see the VELscope Vx Training DVD for more detailed information.

1. Review the patient's relevant medical and dental history.
2. Conduct a thorough extra-oral and intra-oral examination both visually and manually, palpating all the structures of the head and neck.
3. Repeat the intra-oral examination using the VELscope Vx by viewing the oral cavity through the VELscope Handpiece (Figure 1). Maintain a distance of approximately 2 inches (5 cm) from the oral cavity to optimize the visualization of the natural tissue fluorescence.
4. Abnormal tissue typically appears as an irregular, dark area that stands out against the otherwise normal, green fluorescence pattern of surrounding healthy tissue.
5. If a suspicious area is discovered, reevaluate under white light and VELscope trying to identify what might have caused the region to appear abnormal. Take into consideration its appearance under both VELscope and white light, its response to palpation, and salient patient history information.
6. Photo-document any areas of concern both under white light and through the VELscope Vx.
7. Record all relevant findings. Documentation forms are available at www.velscope.com.
8. Inform the patient of all relevant findings and the appropriate course of action.
9. Follow up or refer as appropriate.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

VELscope Vx Step-By-Step Examination Guide

Fluorescence Visualization in the "Normal" Mouth

- Understand what a normal oral cavity looks like under VELscope to best appreciate what may be abnormal.
  - The attached gingiva and anterior tonsillar pillars, for example, often have a naturally darker appearance.
  - Pigmented tissue appearing dark under white light usually also looks dark under VELscope Vx.
- Inflammation typically appears darker under VELscope due to the excess blood content.
- The oral cavity is naturally exposed to varying degrees of chronic irritation and mild inflammation.
  - Due to inflammation, the buccal mucosa, lateral surfaces of the tongue and hard palate may sometimes show darker areas typically characterized by poorly-defined borders.
- Hyperkeratosis may often appear bright under VELscope because of strong keratin fluorescence.

Figure 1. VELscope Vx examination: The clinician shines the blue excitation light into the patient's oral cavity and looks through the VELscope Handpiece

Characteristics that Increase Suspicion of Dysplasia and/or Oral Cancer

- Highly darkened appearance—strong loss of fluorescence
- High-risk location (e.g., lateral/ventral tongue)
- Unilateral presentation
- Asymmetry and/or irregular shape
- Extension over more than one kind of oral structure

Blanching

- Observe the suspicious, typically darker, area through the VELscope Handpiece while applying a light amount of pressure with the back side of an explorer or similar instrument in a sweeping motion to diffuse any blood from the area.
- If the normal green fluorescence returns with this pressure, then the lesion may have an inflammatory component.
- For some important considerations when interpreting the effects of blanching, see the VELscope Vx Training DVD.

Follow-up

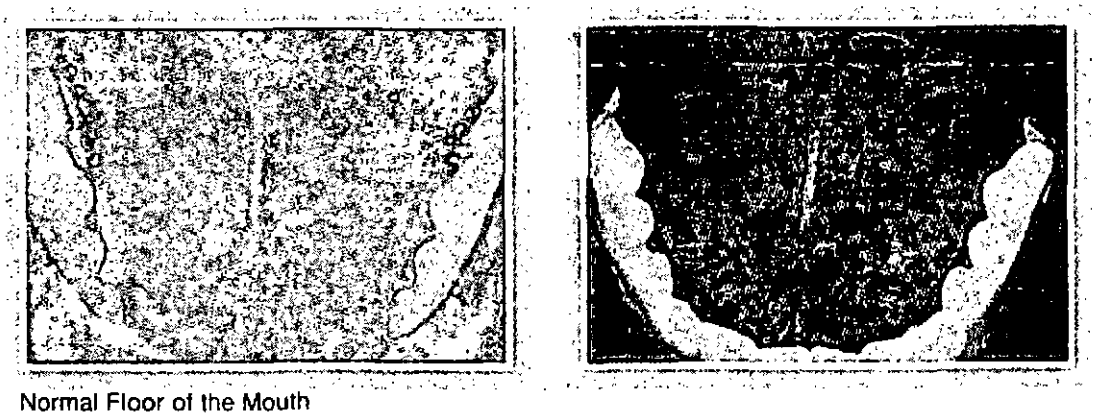
- If a suspicious area cannot be ruled out as benign, it is usually appropriate to perform a follow-up examination (typically in 2 weeks).
- At this time, evaluate whether the suspicious area has changed, especially if the presumed causative agent has been removed.
- If the suspicious area has not cleared up after this follow-up time, use your clinical judgement *and proceed* with further investigation according to the regular standard of care (e.g. referral to a specialist, etc.)

Surgical Biopsy – The Gold Standard

- Remember: the gold standard for diagnosing precancerous and cancerous lesions in the soft tissues of the oral cavity is surgical biopsy.
- A biopsy showing dysplasia is NOT a "false positive"; discovering lesions early in the disease development process allows for the highest probability of a favourable treatment outcome.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Figure 2. Representative examples of the appearance of healthy [illegible] oral tissue under both standard white light and VELscope examination.

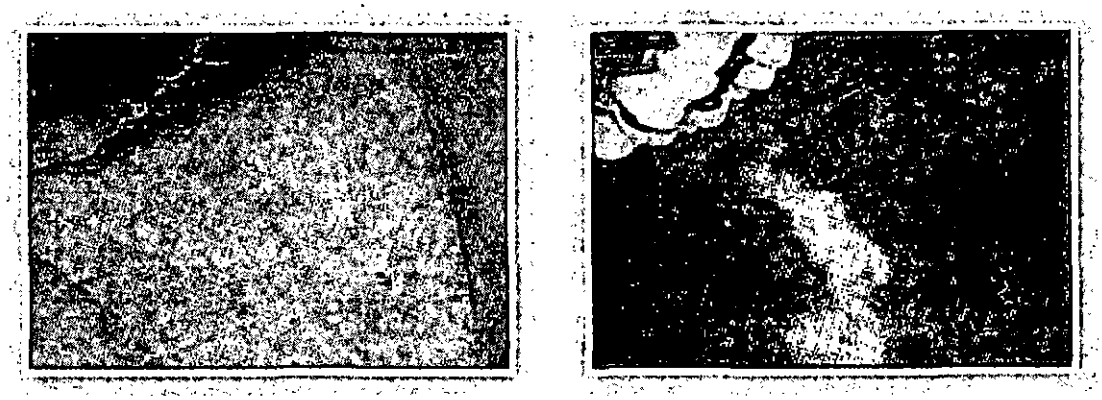


Normal Floor of the Mouth

Sometimes the area around the sub lingual gland can be very [illegible] and can lead to a variable degree of loss of fluorescence.

Normal Variation - Oropharynx with Numerous Lymphoid Aggregates

Sometimes the oropharynx can host variable numbers of lymphoid aggregates, which due to tissue structure, display a pronounced loss of fluorescence.



Irritation and Inflammation

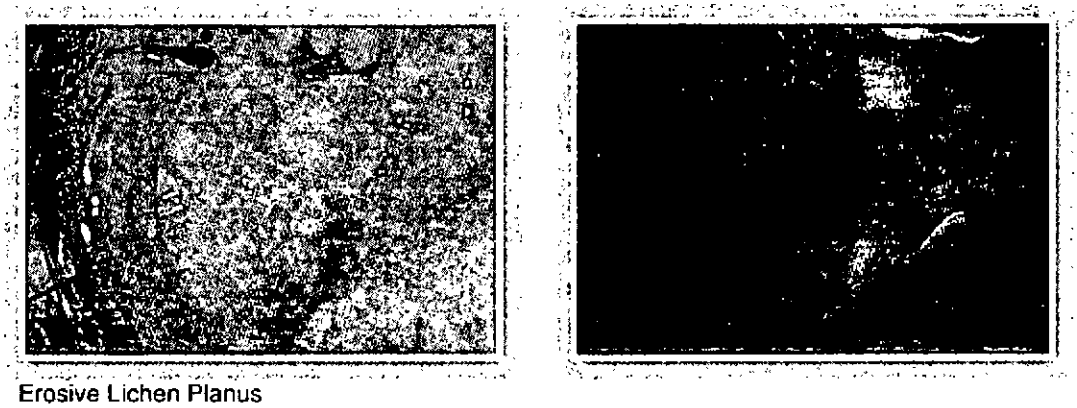
The buccal mucosa is a common site for irritation and consequent inflammation. Inflammation always shows a distinct loss of fluorescence because of increased blood content.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

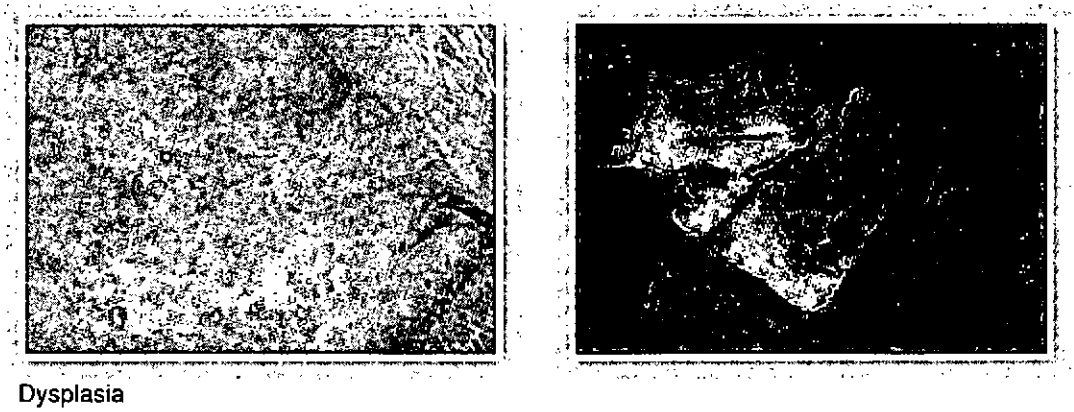
Pigmented Lesions: Amalgam Tattoo

Pigmented lesions show a loss of fluorescence for the same reason that they appear pigmented under white light (absorption of light by the pigment). One should expect the size and shape of the loss of fluorescence to be the same as the size and shape of the pigmentation under white light.



Erosive Lichen Planus

The intense inflammation associated with erosive lichen planus results in a correspondent loss of fluorescence.



Dysplasia

The hyperkeratotic area on the right is an fact dysplastic, and shows a strong loss of fluorescence.

FORWARD [illegible]ENCE LLC

2511 Wind [illegible]
Sugar Land, TX 77459 USA
855-696-7254

VELscope Vx:
The Two-Minute Exam That Could Save Your Life

How many little sores do we find in our mouths? Dozens? Hundreds? More? Most of the time we ignore them and they simply go away.

But sometimes our mouths keep secrets. That's why we use the VELscope Vx Enhanced Oral Assessment system.

Ask us about a VELscope Vx exam.

The VELscope Vx Helps Us:

- Improve our assessment of your overall oral health
- Ensure that the delicate tissues of your mouth are healthy
- Protect you from oral disease, including oral cancer

[illegible]

For more information, please visit www.velscope.com

As seen on
"The Doctors" and ***"Dr. Oz"***

Our dental office is proud to provide the most advanced standards of care available.
Please ask us about a VELscope Vx exam.

VELscope Vx

www.velscope.com

LED Dental Inc
[illegible] Burnaby, BC Canada [illegible]

[illegible] Toll Free +1 888-541-4614
Phone +1 604-434-4614
Fax +1 604-434-4612

Your Mouth Can Hide a Secret...

FORWARD SCIENCE LLC

2511 Wind Fa.. Ln
Sugar Land, TX 77459 USA
855-696-7254

VELscope Vx – for a Clean Bill of Health

- Helps dental professionals find oral mucosal abnormalities, including oral cancer
- Over 10,000,000 examinations performed
- Recognized by the World Health Organization
- The most powerful tool available for assisting in the discovery of oral abnormalities

The VELscope Vx exam: quick painless, effective.

"Adding the VELscope to our diagnostic protocol has been extremely useful and resulted in detection of dangerous lesions that would have otherwise been undetected."

- **Edmond L. Truelove** DMD, MSD Chair & Professor, Oral Medicine, School of Dentistry University of Washington

Oral Cancer and Oral Disease

The VELscope Vx helps us identify oral disease early, while it's still easy to treat.

One of the VELscope's most important tasks is to help locate areas that might, if not treated, progress to oral cancer.

- Found early, oral cancer's 5-year survival rate is good: approx. 83%.
- Found late, oral cancer's 5-year survival rate is poor: approx. 32%
- Clearly, finding oral cancer in its early stages is key to survival

The VELscope Vx offers hope for the early discovery of oral disease, including precancer and cancer.

Risk Factors

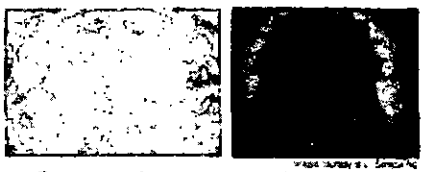
Tobacco and chewing tobacco, along with alcohol, are the leading causes of oral cancer. Over the last four decades, the Human Papilloma Virus (HPV), known for its role in cervical cancer, has been showing up in increasing numbers of oral cancer cases.

"Dentists saving lives? Now more than ever a reality with the development of VELscope. Every dental office needs this instrument."

- **Ken Neuman** DMD, FAGD, FADI, FICD, FACD

Why Use the VELscope Vx?

- The VELscope's blue light stimulates natural fluorescence in the soft tissues of your mouth
- Natural fluorescence, seen through the VELscope Vx, allows dental professionals to see disease not visible with the naked eye
- The VELscope Vx helps us discover oral disease BEFORE it can be seen under ordinary light



Oral disease becomes plainly visible through the VELscope Vx

"I find the VELscope to be an invaluable tool for the detection of oral cancer. The response from my patients has been overwhelmingly positive. In my opinion, this technology will be part of the standard of care in a short period of time."

- **Tony Hewlett, DDS** Standwood, WA

Shining Blue Light on Oral Health™

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

B3. VELscope Clinical Data:

Narrow band (light) imaging of oral mucosa in routine dental patients. Part I: Assessment of value in detection of mucosal changes

Edmond L. Truelove, DDS, MSD • David Dean, DDS • Samuel Maltby • Matthew Griffith
Kimberly Huggins, RDH • Mickealla Griffith, DDS • Stuart Taylor, DDS, MSD

The purpose of this investigation was to determine the value of adding narrow band (light) imaging (NBI) to the standard oral soft tissue examination process used to detect mucosal change. A total of 620 dental patients who came to the clinic for regular dental evaluation or for treatment of acute dental problems were given a standard oral soft tissue examination by dental students under faculty supervision. The results of the white light examination were recorded after the tissues were examined with NBI, at which point areas with a loss of fluorescence (LOF) were recorded. The nature of the tissue change was classified clinically as normal variation, inflammatory, traumatic, dysplastic, or other, and patients were categorized depending on their clinical findings: normal, recall/follow-up visit, or immediate biopsy. Risk factors related to oral dysplasia also were recorded. The addition of NBI added between one and two minutes to the examination process.

Of the 620 examinations, an area with an LOF suggestive of pathology was detected in 69 subjects (11.1%). After a second, immediate evaluation, 29 of the 69 subjects were scheduled for follow-up or biopsy. None of the lesions discovered in these 28 subjects had been detected using standard (white light) examination.

Adding NBI to the routine clinical examination resulted in detection of changes not seen with white light examination in 11.1% of patients; of these, a small but important number were found to have otherwise undetected persistent changes representing inflammatory lesions or potentially dangerous oral dysplasia. Adding NBI as an adjunctive diagnostic procedure improved the quality and outcome of the examination process.

Received: August 31, 2010
Accepted: November 19, 2010

An important component of dental practice is the detection of changes to the oral mucosa and jaws that represent serious threats to health. Among these threats, the risk of oral cancer is a chief concern. Although the overall risk for cancer of the mouth and throat is relatively small, data from the American Cancer Society and National Cancer Institute predict that the lifetime risk of oral cancer is 1 in every 152 females and 1 in every 71 males.[1] The lifetime risk for developing oral cancer is greater than the lifetime risk for cancers of the brain, esophagus, and lymphomas, conditions that receive frequent public scrutiny as important risks for reduction in life expectancy.[1] Oral cancer also is a significant problem because survival rates have improved only marginally during the past 50 years, with the five-year survival rate still only 53%.[1]

Important risk factors for oral cancer include age, ethnic status, tobacco use, excess alcohol consumption, family history of cancer, and prior cancers.[2] The presence of some types of mucosal change, including leukoplakia, erythroplakia, proliferative verrucous leukoplakia, and lichen planus, also has been associated with an increased risk.[3] Poor oral hygiene and lack of regular dental care are among suggestions as potential risk factors, either because of local inflammatory irritation or because patients with poor access to care do not benefit from earlier detection of mucosal changes.[4] Chronic mucosal infections, including candidiasis, herpes simplex, and human papilloma virus, also have been postulated as causing an increased risk for oral cancer.[5-7]

A factor that could be associated with poor prognosis is a delay in the detection and treatment of early oral cancers; however, data to support that hypothesis are not extensive.[1,8,9] Still, if oral cancer behaves like most other cancers, it is logical to assume that very early detection and treatment is likely to result in better survival than delayed detection, which usually is associated with wider spread, metastatic nodes,

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

and regional spread to other organs. Some data exist that identify rates of progression from benign and premalignant to malignant for several types of oral lesions, but little actual data have been collected to demonstrate the value of routine oral examination of patients on reducing the risk of cancer and cancer morbidity.[1,11,12] Some authors have suggested that there is little significant information to support the use of routine oral examination as a valuable tool to reduce morbidity or mortality.[13]

One of the difficulties associated with the clinical assessment of patients who could be at risk for oral cancer is that, until very recently, the only diagnostic method available has been visual and tactile examination of the oral mucosa. While that diagnostic process is reasonable, it cannot detect cellular changes that have not evolved enough to be visible to the unaided eye.

In the past, cancer detection and surveillance in other organ systems have suffered from the same limitations, with purely clinical observations proving to be inadequate in detecting premalignant or early malignant changes. Two excellent examples include the poor predictive value of visual inspection of the uterine cervix and breast self-examination. Until initiation of colposcopy and Pap smear evaluation of the cervix, cancer rates and deaths were significantly higher, while mammography has greatly improved detection and survival of patients with breast cancer.[14,15] All three techniques are considered adjunctive diagnostic procedures designed to provide data to the clinician which, when included in a symptom report and risk factor assessment, can lead to more effective decision-making about the likelihood that a finding represents a potential neoplastic process that requires a biopsy or other more sophisticated diagnostic procedures.

Fig. 1. Clinical photograph of the lateral tongue.

Fig. 2. Photograph of the same area as in Figure 1, demonstrating LOF that represents dysplasia.

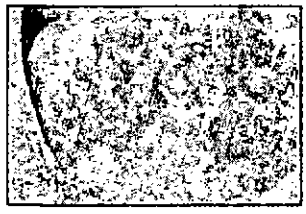


Fig. 3. Clinical photograph of the ventral tongue, showing normal to slightly atypical mucosa.

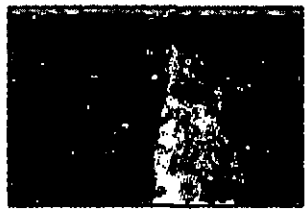


Fig. 4. Photograph of the same area as in Figure 3, demonstrating LOF that represents dysplasia.

The lack of effective adjunctive clinical diagnostic methods has clearly limited the ability of dental professionals to detect very early changes that could predict the presence of emerging inflammatory, premalignant, and dysplastic changes, leaving only visual inspection as the chief diagnostic tool. After visual detection of an observable change in the mucosa, clinicians have had access to two adjunctive diagnostic tools and one definitive tool to guide their decision-making: cytology, toluidine blue tissue staining, and biopsy.[16,17] These methods have helped clinicians to decide whether a finding deserves more careful follow-up and management, and while all three methods remain important and valuable, they still are limited due to their dependence on the presence of visible tissue changes to alert the clinician that further assessment is needed.

Methods to improve early detection of mucosal changes prior to their progression to a frank, clinical lesion state could improve prognosis and limit the morbidity associated with treatment. Narrow band (light) imaging (NBI) of tissues has been used extensively in other areas of the body as a means of identifying tissue changes that are either not visible to the unaided eye or uncharacteristic of a neoplastic process.[18-20] This method has been used to evaluate bronchial tissues and the mucosa of the intestinal tract, with findings that have demonstrated its potential utility.[19,21]

Recently, studies funded by the NIH have investigated the use of NBI for the detection of changes

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Fig. 5. Clinical photograph of herpes simplex of the palate.

Fig. 6. Photograph of the same area as in Figure 5, demonstrating LOF that represents acute inflammation.

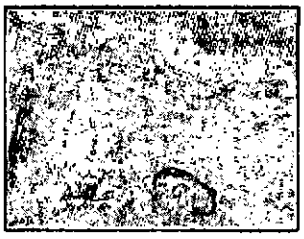


Fig. 7. Clinical photograph of the anterior tonsillar pillar demonstrating lymphoid tissues.

Fig. 8. Photograph of the same area as in Figure 7, demonstrating LOF that represents chronic inflammatory change.

in the oral mucosa associated with neoplasia or premalignant cellular change.[21,22] These studies have shown that NBI has value in the detection of malignant disease and in the determination of surgical margins.[23] One result of these studies has been the development, FDA approval, and marketing of a NBI instrument, VELscope (LED Dental Inc.), that is designed for use in general practice settings.[24] Similar instruments are currently under development.

NBI uses a blue light directed at the oral mucosa and observed through an eyepiece that filters the light. Tissues with different physical, vascular, and cellular characteristic reflect or absorb the blue light, resulting in an image as viewed through the scope with different visual characteristics. The blue light augments the fluorescence properties of some tissue components, generating a green-white appearance. On the other hand, the optical characteristics of some tissues result in a loss of fluorescence (LOF), causing a dark pattern when the tissues are observed through the scope. Inflamed and highly vascularized tissues absorb the light and appear dark compared to the same tissue without inflammation. Oral dysplasia and oral cancer also absorb the light and appear darker than the corresponding tissue without cancer or dysplasia. Dysplastic tissues with significant keratinization (leukoplakia) can exhibit increased fluorescence (whiteness) with LOF (darkness) around the periphery of the lesion. Obviously, because inflammatory lesions absorb the light and appear dark, traumatic, viral, and aphthous lesions demonstrate an LOF, as do migratory glossitis and lymphoid tissue (Fig. 1–8).

Critics of the use of NBI have argued that the results are not sensitive or specific enough and can result in "false positive" findings that cause patients to be at risk for unnecessary invasive procedures.[24,25] Others argue that the use of such adjunctive diagnostic devices is not necessary because risky mucosal changes are visible and can be detected with the unaided eye.[26]

The difficulty with those opinions is that very early changes at the cellular level occur before the gross physical characteristics of the tissue have changed enough to create a clearly visible lesion that, when seen by the clinician, registers as a potentially important inflammatory or dysplastic lesion. Also, most adjunctive diagnostic methods are merely that—adjunctive—and are not intended to be definitive diagnostic tests. Application of strict standards of sensitivity and specificity in judging the relative value of these adjunctive methods could underestimate their potential for guiding the initial clinical decision-making as part of an overall assessment algorithm. Their chief use is to help clinicians discover changes that otherwise might not be observed or be of such a subtle nature that the clinician disregards the potential significance of the finding.

One study that assessed the value of NBI and toluidine blue in determining the nature of clinically detected lesions in a large group of adults who received oral examinations concluded that use did not improve the diagnosis of oral cancer; however, NBI was applied to only those patients who had clearly detectable oral lesions rather than being used as an adjunctive diagnostic process for all of

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

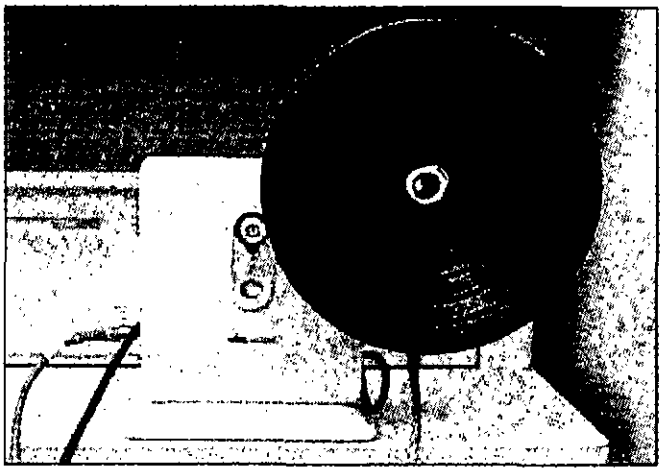


Fig. 9. VELscope with light shield.

the examinations.[21] Had this been done, it is likely that more cases of early dysplasia would have been detected. Application of the technology on all patients could have helped the examiners to identify changes that otherwise would have escaped recognition because of their nonspecific characteristics or lack of progression to a clearly visible state. Unfortunately, only a few studies have evaluated the application of NBI in routine dental practice, but one study has shown detection of premalignant changes that otherwise would have escaped detection.[27]

Objectives

The purpose of this study was to evaluate the value of adding NBI of the oral mucosa for the detection of tissue changes to a standard oral examination in routine dental patients. The study also aimed to assess the relative value of NBI in the detection of inflammatory, dysplastic, and other tissue changes. The goal of the study was to assess the value of adding NBI for the detection of oral changes not readily seen during normal, white-light examination of the oral mucosa. The purpose of the study was not to determine the absolute value of NBI in the detection of oral dysplasia or oral cancer, but to assess whether its use as an adjunctive diagnostic method adds value to standard examination processes. The study also was designed to test the value of this adjunctive method after only a brief examination to determine its value in normal general practice settings, rather than in settings where the modality would be employed by experts who regularly engage in diagnosis and management of mucosal lesions.

Materials and methods

Subjects

Patients seeking routine dental care or treatment for dental symptoms (pain, toothache, and so forth) were invited to participate in the study protocol. The study was approved as a quality improvement study by the institutional review board of the University of Washington, and all patients entered into the study and signed consent after being informed of the study by one of the study investigators.

Study protocol

The study protocol included the following elements: Introduction of the patient to the study and obtaining consent to participate; routine social, medical, and dental histories; a head and neck physical examination, oral soft tissue assessment, and dental examination; recording of visual findings using a data collection form, scoring of tissue changes, and level of dysplasia suspicion (0–4); examination of mucosal tissues using a narrow band light source (VELscope), followed by recording the findings; scoring of type of tissue change and level of dysplasia suspicion (again, on a 0–4 scale); recording follow-up designations as None, Two-week, Four-week, Biopsy Next Visit, Biopsy This Visit, and Other; and recording of risk factors, including none, tobacco, alcohol, immunosuppressive disorder, immunosuppressive medication, cancer history, diabetes, and family history of cancer.

All patients were examined initially by third- and fourth-year dental students, then by the attending faculty of the clinic. Students were provided with a tutorial on conduct of the clinical and NBI methods with examples of normal findings, normal variation, changes caused by inflammatory disorders, and changes caused by dysplasia. The faculty of the clinic was provided with the same information as the students in a computer-based tutorial format. In addition, students and faculty were provided with an instruction packet for each patient enrolled in the study that

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

described the quality assurance study methodologies in addition to containing illustrated scoring sheets. Photographs of normal, variations of normal, and abnormal findings were provided digitally and in printed illustrations. The tutorial activity encompassed approximately one hour of information and instruction.

To facilitate efficiency, a total of five VELscopes were stationed in the clinic, which has a total of 12 operatories, and students accessed the VELscopes as they finished the clinical examination. Faculty supervised use of the VELscopes and interpretation of the clinical and NBI findings. The NBI was not carried out under the most ideal conditions because the clinic is a large, open facility and it was not possible to reduce the ambient room light. For this reason, each VELscope was fitted with a 12- or 14-inch black plastic disc with a hole in the center for the scope. This shield created a large shadow over the patient's mouth, greatly improving visualization for LOF; however, the viewing environment still was not as ideal as it would have been with the room light reduced. Nevertheless, this approach allowed for the detection of many areas of LOF. Figure 9 illustrates the VELscope equipped with the black shield for use in rooms that could not be completely dimmed.

Results

Five percent of subjects declined participation in the study after reading the consent form and discussing the study with an investigator. The most typical reason for a patient declining was concern that the light could cause harm or fear that an abnormality would be detected. Overall, patients were very accepting of the procedure and expressed great appreciation that an adjunctive noninvasive diagnostic aid was available for their evaluation. The addition of the NBI protocol to the examination process added one to two minutes to the visit, not including the study consent process that is not part of a routine diagnostic procedure. Many patients reported personal experiences with friends or relatives who had developed oral cancer and other diseases of the mouth and commented positively about the thorough process being employed at the clinic.

Table 1. Oral cancer risk factors for patients in this study (n = 620).

Risk factor	Percentage of all patients enrolled	Percentage of patients with significant LOF (n = 28)
Current tobacco use	21.5	32.1
Prior tobacco use	15.5	21.0
History of excess alcohol use	3.5	5.0
Poor oral hygiene	14.5	15.6
Diabetic in active treatment	9.5	11.5
History of any type of cancer	9.0	12.5
History of autoimmune disease or immunosuppressive medication	7.5	14.2

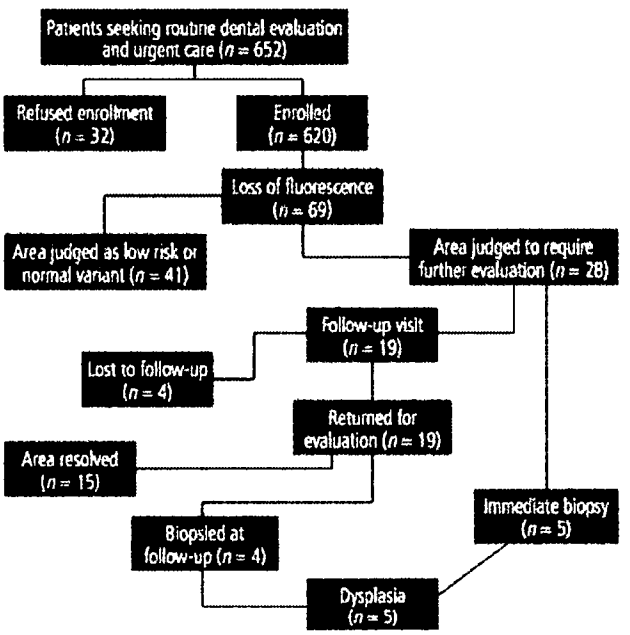
Patients ranged in age from 18–85, and 55% of the 620 patients were women. Of the patients who reported tobacco use, 21.5% reported active use and 15.5% reported prior tobacco use, with only a few patients reporting the use of smokeless tobacco. Nine percent of patients reported a prior history of some type of cancer, and 57% reported a family history of cancer. Nine percent of patients were diabetic and currently under treatment, while 7.5% identified themselves as having an immunological disorder or having used an immunosuppressive medication (Table 1).

LOF in areas that were reported as normal during the white light examination was detected in 69 patients. After immediate re-evaluation, 41 patients were determined to have a region of subtle LOF that could be explained by normal variations in tissue characteristics, while 28 patients were scheduled for either immediate biopsy or a follow-up appointment. Five of those patients agreed to an immediate biopsy and four decided to follow up with their primary dental provider. The remaining 19 patients were scheduled for follow-up in two weeks. Of the 15 patients who returned for reassessment, the area of LOF had resolved and no clinical or NBI abnormality could be detected for 11 of them; this left four patients with persistent LOF compared to corresponding tissues. These LOF sites were biopsied in the same manner as the sites in the five patients who agreed to an immediate biopsy.

In all, nine patients (five during the initial assessment and four at the follow-up visit) were found to have tissue changes detected with NBI, but not white light, that were significant enough when considered in conjunction with the patient's history to require further diagnostic assessment. After the findings and risks were explained in addition to the alternatives to biopsy, all nine patients consented to biopsy,

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Chart 1. Flow diagram of the study results.



although two of them received the biopsy at another facility due to insurance issues.

Of the nine patients who underwent biopsy, three were classified by histopathological assessment as having mild dysplasia and two were classified as having mild to moderate dysplasia (Chart 1). Two other patients were diagnosed as being histologically compatible with lichen planus, and the remaining two patients had inflammatory lesions (Table 2). Lesions detected during the white light examination are not included in this discussion and were handled in the routine manner used to manage visible oral lesions. The five dysplastic lesions that were detected with NBI were located in the buccal mucosa, the lateral border of the tongue, the lip, the palate, and the alveolar ridge.

The white light examination resulted in the detection of a variety of soft tissue lesions of the mucosa, but this study did not focus on those that were easily detected using standard visual inspection techniques. For the sake of completeness, a brief summary of the types of soft tissue lesions encountered using white light and NBI is listed in Table 3. These lesions included cheek bites, aphthous ulcers, herpetic lesions, migratory glossitis, fissured tongue, lichen planus, inflamed minor salivary duct openings, candidiasis, and cheilitis. Tonsillitis, pharyngitis, papillomas, scars, leukoplakia, and draining abscesses also were detected. Those lesions with inflammatory components demonstrated LOF, and in most cases the LOF provided a more dramatic presentation of the extent and severity of the inflammatory change than the clinical examination did (Fig. 5–8).

The mucosal changes detected with white light, both white light and NBI, or NBI only were widely distributed throughout the mouth, with no distinct difference in pattern noted between the two different methods of assessment.

As previously described, a number of patients had mucosal changes detected with one or both types of visual assessments. Changes were noted in nearly half of all patients (305 of 620); however, the vast majority of them were found to be normal or minor variants and did not appear to represent significant pathology. The most common lesion was cheek bite, while the second most common was trauma to the tongue. Inflammatory changes to the oropharyngeal and tonsil areas also were common. Cheilitis and changes to the epithelium of the lips also were common and represented a range of etiologies that included habitual lip biting and actinic changes of the lower lip. A number of cases of lichen planus and generalized glossitis also were detected during the white light examination.

Although the study size was reasonably large, the diverse nature of lesions found and the wide range of risk factors associated with the development of oral lesions precluded development of specific associations between risk of mucosal change and a host of factors, including age, gender, tobacco use, diabetes, immunodeficiency, immunosuppressive medications, cancer history, family cancer history, and oral health status. Nevertheless, it is interesting to note that the patients with changes detected with white light, NBI, or both were more likely to carry one or more of the risk factors compared to those who had no areas of mucosal

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Table 2. Biopsy results.

Lesion diagnosis	Number of patients
Lichen planus	2
Inflammation	2
Mild dysplasia	3
Mild to moderate dysplasia	2

Table 3. Types of lesions detected with combined clinical and NBI diagnosis methods.

Type of mucosal lesion detected	Relative frequency
Traumatic injury	Common
Lichen planus	Occasional
Dysplasia	Rare*
Cheilitis	Common
Migratory glossitis	Occasional
Fissured tongue	Occasional
Pharyngitis and tonsillitis	Common
Herpes simplex	Occasional
Recurrent aphthous	Occasional
Candidiasis	Occasional
Leukoplakia	Occasional
Mucosal bacterial infections	Rare
Inflamed minor salivary ducts	Occasional

Common = ≥10% or greater; occasional = <10%; rare = <1%.
*Near 1% prevalence in this study's population.

change, with 54 of 69 patients (78%) who demonstrated LOF having either a history of tobacco use or current tobacco use. Those with mucosal lesions also were more likely to have poor oral hygiene.

Discussion

The purpose of this quality improvement study was to gain information about the clinical utility of one simple adjunctive diagnostic method (NBI) for the detection of mucosal changes. The rationale for the study assumed that such a diagnostic adjunctive method is not necessary to detect mucosal changes readily seen with normal white light examination methods. Existing data suggest that current examination methods are not sufficient for the earliest detection of mucosal changes that could represent inflammatory damage or the presence of very early dysplasia. This could partly account for the only modest reduction in oral cancer deaths since 1960.[1,13]

There are several possible explanations for why oral cancer deaths and the stage of oral cancer at the time of diagnosis have not changed dramatically in the past 50 years.[1] The lack of improvement could relate to a number of factors, but when considering that the percentage of the population that receives regular dental care has increased in the past 50 years, it appears obvious that current diagnostic methods could benefit from one or more adjunctive approaches. Early detection of dysplasia in other organ systems has been acknowledged to be an important component in improving survival, so it is difficult to believe that early detection of potentially significant mucosal changes, whether they are inflammatory or dysplastic, would not lead to improvements in cancer-related outcomes.

Because oral cancer is a relatively uncommon condition, the authors did not expect to detect a large number of cases of dysplasia with either the white light examination or the use of NBI and were surprised that five cases of early dysplasia were identified. Of additional interest is the observation that NBI detected many areas of inflammation and vascular change not identified during the white light examination, suggesting that this methodology also could be useful in cataloguing instances of chronic irritation and inflammatory change that, over time, could lead to irreversible conditions such as fibrosis, scarring, and leukoplakia.

While some might be concerned that detection of five unobserved cases of dysplasia seems higher than would normally be expected, it is important to point out that most experts believe that cellular atypia and early stages of dysplasia might not uniformly progress to more severe stages of oral cancer and that several cases of dysplasia exist for each case of oral cancer.[6,31] Therefore, it is not quite so surprising that the rate of dysplasia found in the current study was 0.8%. American Cancer Society statistics state that the lifetime risk for developing oral cancer is less than 1 in 90, or approximately 1%, a figure not far from the 0.8% found in the population in the current study.[27] On the other hand, the rate detected in the current study might have been higher than expected among

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

routine dental patients seen in private practice settings because more than 60% of the patients enrolled in the study were seeking urgent care and might have had more risk factors (tobacco, poor oral hygiene, systemic disease, and so forth) than normal dental populations.

The study methodology was limited because it was carried out in a clinical setting that did not allow for a reduced ambient light examination environment. Based on the authors' experience in the use of NBI in darker settings, it is likely that a number of lesions viewed at the clinic with LOF went undetected. It is possible that one or more of these lesions might even have been dysplastic or an inflammatory change that could have benefited from further follow-up.

The study also was limited because the authors deliberately decided to use relatively inexperienced examiners, which might have resulted in lower rates of detection of mucosal changes for either method. The authors wanted to test the use of NBI in an environment that resembled a general dental setting more than a specialty clinic that focuses on the detection of mucosal lesions and disease. To that end, the results demonstrate the value of NBI when added to routine examination methods.

The study also could have been limited because it occurred in a university setting, where students and attending faculty might be more focused on mucosal assessment processes. A larger, multiple private office study would be useful, with general dentists and dental hygienists providing the white light and NBI process during normal patient care for both new and recall patients. It is encouraging, however, that this adjunctive diagnostic aid appeared to improve the detection of mucosal changes not easily visible with white light examination.

The authors were pleased that adding the NBI to the examination process did not significantly increase the time required to evaluate patients when the study consent process was excluded. The authors also were pleased that patient response was strongly positive and that the study appeared to raise awareness among patients that the dental examination process extends beyond purely odontogenic issues and can encompass the detection of disorders that could have more severe and wider implications on their health.

Conclusion

The findings of this study support the use of NBI as a simple adjunctive diagnostic device that, when used as one component of a standard diagnostic protocol, could help clinicians to detect inflammatory and dysplastic tissues. Use of this technology could improve clinicians' ability to monitor and follow initially detected changes, and to better judge progression versus resolution and response to nonsurgical treatments. These findings need to be further explored in other settings to determine overall utility in general practice, but based on these findings, NBI appears to have the potential to assist general practitioners in assessment and decision-making related to mucosal tissues and lesions.

Acknowledgements

This study was made possible with funding from NIH grant #T32 DE07132 and LED Dental Inc.

Author Information

Dr. Truelove is a professor, Department of Oral Medicine, University of Washington, Seattle, where Dr. Taylor is a part-time faculty member and director of the urgent care clinic, Dr. Griffith is a full-time faculty member and teaches in the Diagnosis and Urgent Care Clinic, Ms. Huggins is a full-time affiliate faculty member and a member of the professional staff in the departments of Oral Medicine and Dental Public Health, and Mr. Maltby and Mr. Griffith are senior dental students. Dr. Taylor also maintains a private practice of oral medicine in Federal Way, WA. Dr. Dean is in private practice in Bellevue, WA.

References

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK, eds. SEER cancer statistics review, 1975-2008. Bethesda, MD: National Cancer Institute;2010. Available online at: http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER website, 2011.
2. Divaris K, Olshan AF, Smith J, Bell ME, Weissler MC, Funkhouser WK, Bradshaw PT. Oral health and risk for head and neck squamous cell carcinoma: The Carolina Head and Neck Cancer Study. Cancer Causes Control 2010;21(4):567-575.
3. Jeber MA. Oral epithelial dysplasia in non-users of tobacco and alcohol: An analysis of clinicopathologic characteristics and treatment outcome. J Oral Sci 2010;52(1):13-21.
4. Wang YP, Chen HM, Kuo RC, Yu CH, Sun A, Liu BY, Kuo YS, Chiang CP. Oral verrucous hyperplasia: Histologic classification, prognosis, and clinical implications. J Oral Pathol Med 2009;38(6):651-656.
5. Szarka K, Tar I, Feher E, Gall T, Kis A, Toth ED, Boda R, Marton I, Gergely L. Progressive increase of human papillomavirus carriage rates in potentially malignant and malignant oral disorders with increasing malignant potential. Oral Microbiol Immunol 2009;24(4):314-318.
6. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa: Terminology, classification and present concepts of management. Oral Oncol 2009;45(4-5):317-323.
7. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral infections and dental factors in relation to oral cancer: A Swedish case-control study. Eur J Cancer Prev 1998;7(3):201-206.
8. Yang SW, Lee YS, Chen TA, Wu CJ, Tsai CN. Human papillomavirus in oral leukoplakia is no prognostic indicator of malignant transformation. Cancer Epidemiol 2009;33(2):118-122.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

9. Gardolfo S, Castellani R, Pentenero M. Proliferative verrucous leukoplakia: A potentially malignant disorder involving periodontal sites. J Periodontol 2009;80(2):274-281.
10. Stamagas M, Breen TL, LeRoith D. Update on diabetes mellitus: Prevention, treatment, and association with oral diseases. Oral Dis 2008; 14(2):105-114.
11. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: An overview of the literature. J Oral Pathol Med 2008;37(1):1-10.
12. Weijers M, Ten Hove I, Allard RH, Bezemer DP, van der Waal I. Patients with oral cancer developing from pre-existing oral leukoplakia: Do they do better than those with *de novo* oral cancer? J Oral Pathol Med 2008;37(3):134-136.
13. Sherman AG, Ertezaei P, Chernin AS, Wallace NE, Taylor JM, Hogikyan ND. Demographics and efficacy of head and neck cancer screening. Otolaryngol Head Neck Surg 2010;143(3):353-360.
14. Pimple SA, Amin G, Goswami S, Shastri SS. Evaluation of colposcopy vs. cytology as secondary test to triage women found positive on visual inspection test. Indian J Cancer 2010;47(3): 308-313.
15. Ahmed NU, Haber G, Semenya KA, Hargreaves MK. Randomized controlled trial of mammography intervention in insured very low-income women. Cancer Epidemiol Biomarkers Prev 2010;19(7):1789-1798.
16. Gupta A, Singh M, Ibrahim R, Mehrotra R. Utility of toluidine blue staining and brush biopsy in precancerous and cancerous oral lesions. Acta Cytol 2007;51(5):788-794.
17. Mehrotra R, Singh MK, Pandya S, Singh M. The use of an oral brush biopsy without computer-assisted analysis in the evaluation of oral lesions: A study of 94 patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106(2):246-253.
18. Lee CT, Chang CY, Lee YC, Tai CM, Wang WL, Tseng PH, Hwang JC, Hwang TZ, Wang CC, Lin JT. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy 2010;42(8):613-619.
19. Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: A meta-analysis. Endoscopy 2010;42(5):351-359.
20. Kataeda C, Tanabe S, Kozuma W, Higuchi K, Sasaki T, Azuma M, Kataeda N, Masaki T, Nakayama M, Okamoto M, Muto M. Narrow band imaging for detecting superficial squamous cell carcinoma of the head and neck in patients with esophageal squamous cell carcinoma. Endoscopy 2010;42(3):185-190.
21. Poh CF, Zhang L, Anderson DW, Durham JS, Williams PM, Priddy RW, Berean KW, Ng S, Tseng OL, MacAulay C, Rosin MP. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. Clin Cancer Res 2006;12(22):6716-6722.
22. Poh CF, Ng SP, Williams PM, Zhang L, Laronde DM, Lane P, Macaulay C, Rosin MP. Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. Head Neck 2007;29(1):71-76.
23. Poh CF, Zhang L, Anderson DW, Durham JS, Williams PM, Priddy RW, Berean KW, Ng S, Tseng OL, MacAulay C, Rosin MP. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. Clin Cancer Res 2006;12(22):6716-6722.
24. Mehrotra R, Singh M, Thomas S, Nair P, Pandya S, Nigam NS, Shukla P. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc 2010;141(2):151-156.
25. Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: A systematic review of the literature. J Am Dent Assoc 2008;139(7):896-905.
26. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277-300.
27. Huff K, Stark PC, Solomon LW. Sensitivity of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice. Gen Dent 2009;57(1):34-38.

Manufacturers

LED Dental Inc., Burnaby, British Columbia, Canada
888.541.4614, www.velscope.com

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Clinical Cancer Research Vol. 12, 6716-6722, November 15, 2006

(VELscope)

11/24/2006

Vancouver, British Columbia, Canada

Catherine F. Poh et al.

Purpose:
Genetically altered cells could become widespread across the epithelium of patients with oral cancer, often in clinically and histologically normal tissue, and contribute to recurrent disease. Molecular approaches have begun to yield information on cancer/risk fields; tissue optics could further extend our understanding of alteration to phenotype as a result of molecular change.

Experimental Design:
We used a simple hand-held device in the operating room to directly visualize subclinical field changes around oral cancers, documenting alteration to fluorescence. A total of 122 oral mucosa biopsies were obtained from 20 surgical specimens with each biopsy being assessed for location, fluorescence visualization (FV) status, histology, and loss of heterozygosity (LOH; 10 markers on three regions: 3p14, 9p21, and 17p13).

Results:
All tumors showed FV loss (FVL). For 19 of the 20 tumors, the loss extended in at least one direction beyond the clinically visible tumor, with the extension varying from 4 to 25 mm. Thirty-two of 36 FVL biopsies showed histologic change (including 7 squamous cell carcinoma/carcinomas in situ, 10 severe dysplasias, and 15 mild/moderate dysplasias) compared with 1 of the 66 FV retained (FVR) biopsies. Molecular analysis on margins with low-grade or no dysplasia showed a significant association of LOH in FVL biopsies, with LOH at 3p and/or 9p (previously associated with local tumor recurrence) present in 12 of 19 FVL biopsies compared with 3 of 13 FVR biopsies ($P = 0.04$).

Conclusions:
These data have, for the first time, shown that direct FV can identify subclinical high-risk fields with cancerous and precancerous changes in the operating room setting.

Authors:
Catherine F. Poh1,2,3, Lewei Zhang1, Don W. Anderson5, J. Scott Durham5, P. Michele Williams1,3, Robert W. Priddy1, Ken W. Berean6, Samson Ng1, Olivia L. Tseng7, Calum MacAulay4 and Miriam P. Rosin2,7

Authors' affiliations:
1 Faculty of Dentistry, University of British Columbia, Departments of 2 Cancer Control Research, 3 Oral Oncology, and 4 Cancer Imaging, British Columbia Cancer Agency, Departments of 5 Surgery (Otolaryngology) and 6 Pathology, Vancouver General Hospital, Vancouver, British Columbia, Canada, and 7 School of Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada

OCF Note:
The device mentioned in the above article is being sold in the US as the VELscope.

Imaging, Diagnosis, Prognosis

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Fluorescence Visualization Detection of Field Alterations in Tumor Margins of Oral Cancer Patients

Catherine F. Poh[1,2,3], Lewei Zhang[1], Don W. Anderson[5], J. Scott Durham[5], P. Michele Williams[1,3], Robert W. Priddy[1], Ken W. Berean[6], Samson Ng[1], Olivia L. Tseng[7], Calum MacAulay[4] and Miriam P. Rosin[2,7]

Authors' Affiliations: [1] Faculty of Dentistry, University of British Columbia, Departments of [2] Cancer Control Research, [3] Oral Oncology, and [4] Cancer Imaging, British Columbia Cancer Agency, Departments of [5] Surgery (Otolaryngology) and [6] Pathology, Vancouver General Hospital, Vancouver, British Columbia, Canada, and [7] School of Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada

Requests for reprints: Miriam P. Rosin, BC Oral Cancer Prevention Program, BC Cancer Agency/Cancer Control Research Centre, 675 West 10th Avenue, Vancouver, British Columbia, Canada V5Z 1L3. Phone: 604-675-8078; Fax: 604-675-8180; E-mail: Miriam_Rosin@shaw.ca.

Abstract

Purpose: Genetically altered cells could become widespread across the epithelium of patients with oral cancer, often in clinically and histologically normal tissue, and contribute to recurrent disease. Molecular approaches have begun to yield information on cancer/risk fields; tissue optics could further extend our understanding of alteration to phenotype as a result of molecular change.

Experimental Design: We used a simple hand-held device in the operating room to directly visualize subclinical field changes around oral cancers, documenting alteration to fluorescence. A total of 122 oral mucosa biopsies were obtained from 20 surgical specimens with each biopsy being assessed for location, fluorescence visualization (FV) status, histology, and loss of heterozygosity (LOH; 10 markers on three regions: 3p14, 9p21, and 17p13).

Results: All tumors showed FV loss (FVL). For 19 of the 20 tumors, the loss extended in at least one direction beyond the clinically visible tumor, with the extension varying from 4 to 25 mm. Thirty-two of 36 FVL biopsies showed histologic change (including 7 squamous cell carcinoma/carcinomas *in situ*, 10 severe dysplasias, and 15 mild/moderate dysplasias) compared with 1 of the 66 FV retained (FVR) biopsies. Molecular analysis on margins with low-grade or no dysplasia showed a significant association of LOH in FVL biopsies, with LOH at 3p and/or 9p (previously associated with local tumor recurrence) present in 12 of 19 FVL biopsies compared with 3 of 13 FVR biopsies ($P = 0.04$).

Conclusions: These data have, for the first time, shown that direct FV can identify subclinical high-risk fields with cancerous and precancerous changes in the operating room setting.

In 1953, Slaughter published a hallmark article in which he emphasized the importance of examining the field surrounding oral cancers for both risk assessment and management of this disease (1). There has been extensive research in this area since then, more recently, using molecular technology. It is becoming increasingly apparent that genetically altered cells could become widespread across the epithelium of patients with oral cancer, into clinically and histologically normal tissue, and that these cells could drive the process of field cancerization (2, 3). In recognition of this, surgeons try to remove oral squamous cell carcinomas (SCC) with a significant width of surrounding normal-looking oral mucosa, if anatomically allowed. However, the occult disease varies in size and a wealth of evidence suggests that it frequently extends beyond the tumor clearance. This extension may be responsible for the high rate of recurrence of carcinomas at the primary site (~10-30% of cases; refs. 4–9). There is a pressing need to develop new approaches that can be easily used in clinical practice to facilitate the detection of these clinically occult fields.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

One such new approach may involve the use of tissue optics. The association of cancer development with the loss of normal tissue autofluorescence has been reported for a number of tissues and organs (10–15). More recently, visual aids using optical methods to detect such loss have been shown to reveal premalignant and malignant lesions that are not detected by unaided eyes (16–18). We have reported the development of a simple hand-held device that facilitated the detection of autofluorescence loss in both visible and occult high-risk oral lesions through direct fluorescence visualization (FV; refs. 17, 18). The interaction of light with tissue has generally been found to highlight changes in the structure and metabolic activity of the areas optically sampled. Specifically, the loss of autofluorescence is believed to reflect a complex mixture of alterations to intrinsic tissue fluorophore distribution, such as the breakdown of the collagen matrix and a decrease in flavin adenine dinucleotide concentration due to tissue remodeling and increased metabolism associated with neoplastic development. Correspondingly, structural changes in tissue morphology associated with neoplastic development in both the epithelium and lamina propria (e.g., thickening of the epithelium, hyperchromatism and increased cellular/nuclear pleomorphism, or increased microvascularity), lead to increased absorption and/or scattering of light, which in turn, reduces and modifies the detectable autofluorescence (16, 17, 19, 20).

The objective of this study was to investigate the value of this device in the operating room to delineate field change in autofluorescence around cancers by determining and comparing the histopathologic and molecular changes of margin biopsies that retained normal FV with those margin biopsies that showed a loss of FV. We chose microsatellite analysis for loss of heterozygosity (LOH) at 3p, 9p, and 17p as the molecular analysis, a method used by many international groups to mark clonal spread and possibly predict recurrence (21). A recent study showed that detection of LOH at 3p and/or 9p at prior cancer sites (after tumor removal) was strongly associated with tumor recurrence: samples with such loss had a 26.3-fold increase in the risk of developing second oral malignancy at the site compared with those that retained both of these arms (22). This current study showed a frequent loss of FV of varying distances (up to 25 mm) in clinically normal–looking mucosa surrounding the tumors and a strong concordance between loss of autofluorescence in tumor margins and the presence of significant histologic change and molecular risk.

Materials and Methods

Patients. Twenty consecutive patients with biopsy-confirmed primary cancer of the oral cavity were accrued to the study as they presented at the British Columbia Cancer Agency between July 2004 and February 2005. Eligibility criteria included the presence of early stage disease (T_0-T_2) scheduled for surgical excision with intent to cure. All the patients were >18 years of age and provided informed consent.

Of the 20 cases in this study, 65% were male, 65% had a smoking history, and 75% were Caucasian. The average age was 58 (36-80 years). Tumor staging was determined from surgical specimens using American Joint Committee on Cancer Staging criteria (23): eight carcinomas *in situ* (CIS, stage 0) and five stage I and seven stage II invasive SCCs (Table 1). Nine of the SCCs were well to moderately well differentiated with the remaining three poorly differentiated. The majority of the tumors were from the tongue (17 of 20, 85%), with one case from the floor of the mouth, and two from the gum.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Patient ID	Tumor stage	Demographics			Histology* and distance to tumor boundary (mm)†			
		Age	Gender	Ever smoke	Anterior	Medial	Posterior	Lateral
1	0	51	M	Y		11	11	11
2	0	78	M	Y		5		
3	0	57	M	Y	12			5
4	0	78	M	Y			6	
5	0	37	F	N		5	5	
6	0	52	F	Y	11	3		
7	0	74	M	Y	25		7	
8	0	45	F	N		5		
9	I	74	M	N				
10	I	62	M	Y	3			8
11	I	44	F	N	8		8	
12	I	58	M	Y		11		
13	I	57	M	N	4			
14	II	77	M	Y			12	4
15	II	40	F	N	5		12	
16	II	80	F	Y	4	8	4	4
17	II	66	M	Y	3	10	12	
18	II	44	M	Y	16			
19	II	56	F	N	8		12	
20	II	36	M	Y	4			9

*Histology: Cancer (light blue), high-grade dysplasia (red), low-grade dysplasia (yellow), no dysplasia or cancer (green), not applicable (grey), no extension of FVL beyond clinical tumor
†Distance: values reflect the distance from the boundary of clinically apparent tumor to the FVL boundary (mm).

Table 1. Demographics of patients and description of FVL margin biopsies

The FV device. A description of the research FV device and its use is given in Lane et al. (17). Briefly, it consists of a bench-top light source coupled to a hand-held unit for direct visualization. Lesions were illuminated by this blue/violet light source and then directly visualized through long pass and notch filters, which allow the passage of green and red autofluorescence.

Under direct FV, the normal oral mucosa emits various shades of pale green autofluorescence. Clinical lesions that retained the normal green autofluorescence under FV were defined as FV retained (FVR). Tissue which showed a reduction in the normal pale green and appeared as dark patches were classified as FV loss (FVL; see example in Fig. 1C ; ref. 18). This distinction involved a comparison of the lesion site with both adjacent tissue and, as an anatomic control, with tissue on the contralateral side.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

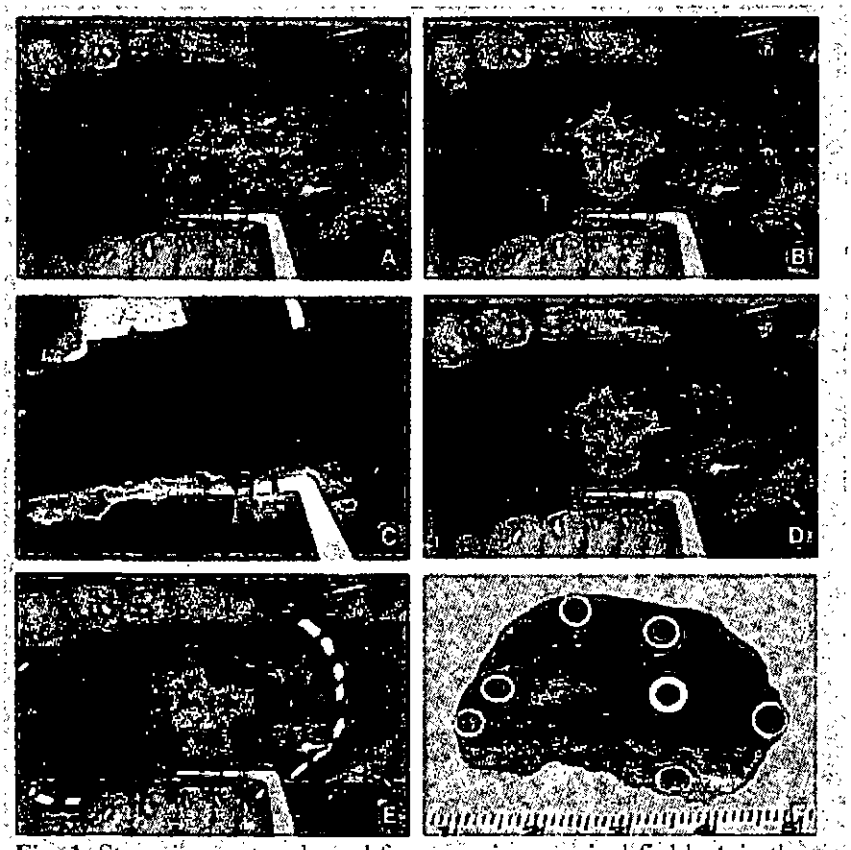


Fig. 1. Stepwise protocol used for assessing surgical field. *A*, in the operating room, initial assessment under white light of an ill-defined SCC at right ventrolateral tongue; *B*, clinically apparent tumor outlined in blue; *C*, assessment of field using FV in the dark; *D*, FVL area outlined in green in the dark; *E*, boundary of surgical specimen (*red*); *F*, blocking of surgical specimen, showing location of punch biopsy sites from clinically visible tumor (*red circle*), from tissue showing FVL, placed directly abutting FVL boundary (*green circle*), and, from tissue showing FVR, placed directly abutting the boundary of surgical specimen (*blue circle*).

Photographs of tissue fluorescence were acquired using illumination from the FV device and a digital single lens reflex camera (Fuji FinePix S2 Pro, Fujifilm, Odawara, Japan) with a long-pass filter (Schott GG475-3, Howard Glass, Worcester, MA). The single lens reflex camera was equipped with a 105 mm f/2.8 macro lens (Nikkor-Micro, Nikon, Tokyo, Japan) and a ring flash (Nikon Macro Speedlight SB-29s, Tokyo, Japan) for white-light images.

Surgical field assessment of FV status. The protocol involved the examination of the surgical site of each patient under both regular operating room illumination and with direct FV, in a stepwise fashion as shown in Fig. 1. All procedures were done while the patient was under general anesthesia and each step was photographed for documentation. The steps included an initial assessment under regular operating room light (Fig. 1A, step 1), demarcation of the boundary of the clinical tumor using a blue marker (Devon skin marker, Ludlow Company, Chicopee, MA) as judged by the surgeon (D.W. Anderson or J.S. Durham; Fig. 1B, step 2), followed by assessment of the site for altered fluorescence using direct FV (Fig. 1C, step 3). The latter examination was done with the light turned off, using the FV device. Areas showing loss of normal green fluorescence were outlined, demarcating FVL

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

boundaries (Sharpie green marker, Sanford, Oak Brook, IL; Fig. 1D, step 4). Then the light was turned back on, the distances between the clinically visible tumor under white light and FVL boundaries were ascertained using a flexible ruler (Devon skin marker, Ludlow) in four directions: anterior, posterior, medial (to the sagittal plane or dorsum tongue), and lateral (to the sagittal plane or floor of mouth margin). Finally, an electroknife was used to outline the surgical boundary (Fig. 1E, step 5).

Tissue sampling and histologic assessment. After resection, a total of 122 punch biopsies (5 mm) were taken from the tumor and from the tumor margins with at least one margin biopsy from each of the four directions (Fig. 1F, step 6 and Fig. 2). All biopsies were fixed in formalin and submitted for histopathologic evaluation by study pathologists without knowledge of FV status (L. Zhang, R.W. Priddy, and K.W. Berean).

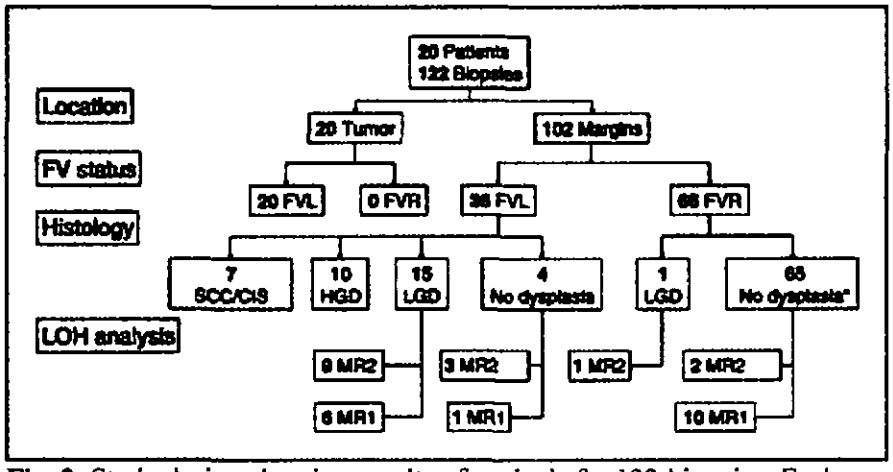


Fig. 2. Study design showing results of analysis for 122 biopsies. Each biopsy is described with respect to location (tumors, margin), FV status (FVR, FVL); histology [SCC, CIS, high-grade dysplasia (HGD), low-grade dysplasia (LGD); no dysplasia], and LOH analysis [presence of patterns previously associated with recurrence; ref. (22): MR1, no LOH at 3p and 9p; MR2, LOH at 3p and/or 9p]. *, 12 cases were randomly selected from FVR margins without dysplasia for LOH analysis.

Microsatellite analysis of tumor margins. All FVL biopsies from the tumor margins with a histologic diagnosis of low-grade dysplasia (15 biopsies) or no dysplasia (4 biopsies) were microdissected and analyzed for LOH (Fig. 2, see LOH analysis). As a control, an additional 13 biopsies were analyzed from FVR margins. The protocols for digestion and extraction of samples, LOH analysis, and scoring are described in Zhang et al. (13). All samples were coded so that LOH analysis was done without knowledge of diagnosis or FV status. Microsatellite markers that were used mapped to the following 10 regions: 3p14.2 (*D3S1234, D3S1228,* and *D3S1300*), 9p21 (*IFNA, D9S171, D9S1748,* and *D9S1751*), and 17p11.2 (*CHRNB1*) and 17p13.1 (*tp53* and *D17S786*). These were markers used in previous studies to predict cancer risk of oral premalignant lesions (8, 22, 24–28).

Statistical analysis. Differences and associations between groups were examined using either Fisher's exact test for categorical variables or *t* test for continuous variables. All tests were two-sided. $P < 0.05$ was considered to be statistically significant.

Results

A total of 122 oral mucosa biopsies were obtained from the 20 tumors, 20 from the clinical tumor

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

itself and 102 from the tumor margins. Figure 2 shows the study design and summarizes biopsy-specific data obtained for location, FV status, histology, and LOH. For each surgical sample, there were three boundaries: the boundary of the clinically apparent tumor (Fig. 1B), the FVL boundary (Fig. 1D), and the surgical boundary (Fig. 1E). Thirty-six margin biopsies were obtained from FVL tissue and these were placed adjacent to the FVL boundary. The 66 FVR margin biopsies were placed adjacent to the surgical boundary (Fig. 1F).

Novel FVL fields extend beyond the clinical boundary. All tumors showed a loss of fluorescence (FVL), regardless of tumor stage and grade of differentiation. In 19 of 20 tumors, FVL boundaries extended beyond the clinically apparent lesion (Table 1). The extent of this subclinical FVL extension varied considerably, ranging from 4 to 25 mm (mean, 10.3 ± 5.7 mm), with 10 tumors showing a >10-mm FVL extension in one or more directions. It is important to note that FVL extension was never evenly distributed around any given tumor. For example, the tumor in Fig. 1 showed subclinical FVL extension primarily in the posterior direction; in contrast, most of the extension in the tumor in Fig. 3 was in the anterior and lateral directions, with minimal extension in the medial and posterior directions.

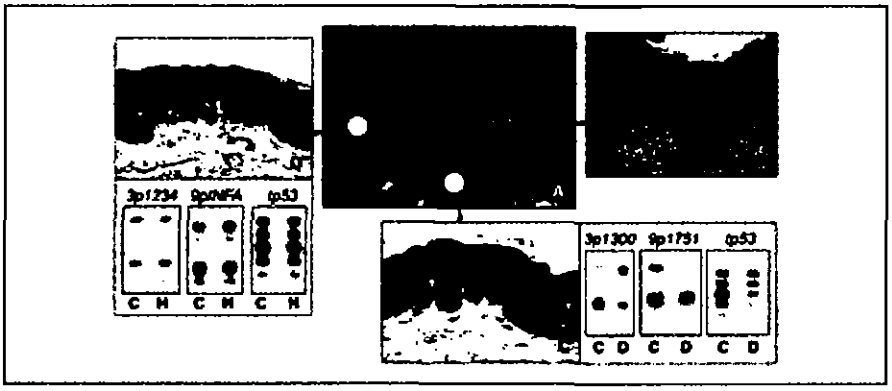


Fig. 3. Presence of high-grade histology or molecular clones in FVL margins outside of clinically apparent tumor. *A,* mapping of surgical field showing three boundaries: clinically apparent tumor (*blue*), FVL boundary (*green*), and boundary of surgical specimen (*red*). *B,* photomicrograph of FVL margin (*red circle*) showing high-grade dysplasia. *C,* photomicrograph and LOH images of FVL margin (*yellow circle*) showing mild dysplasia with LOH at *D3S1300, D91751,* and *tp53. D,* photomicrograph and LOH images of FVR margin (*green circle*) showing no dysplasia and heterozygosity (no LOH) at *D3S1234, D9INFA,* and *tp53.* Magnification, x100.

To investigate the possibility that the advent of invasion is accompanied by a more aggressive lateral/horizontal subclinical FVL spread, we compared the margin mapping data in the 8 preinvasive high-grade lesions (*CIS*) with the 12 invasive SCCs. The average width for subclinical FVL extension beyond the clinical boundary was similar for *CIS* and invasive SCCs (10.4 ± 6.7 versus 10.2 ± 5.6 mm; $P = 0.79$).

FV identifies the majority of histologic risks. As shown in Fig. 2, among the 36 FVL margins, there were 7 (19%) cancers (*CIS*/SCC), 10 (28%) high-grade dysplasias, 15 (42%) low-grade dysplasias, and 4 (11%) cases with no dysplasia. In contrast, only 1 of the 66 FVR margins was dysplastic. In other words, FVL identified 32 of the 33 cancerous or dysplastic biopsies in the 102 margin biopsies, including all of the cancerous and high-grade dysplasias. There was a significant correlation between the presence of high-grade dysplasia and above with loss of FV ($P < 0.0001$).

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Of the 10 tumors showing >10-mm FVL extension at one or several directions of the tumor margins, 6 tumors showed histologic changes of high-grade dysplasia and above in biopsies taken from FVL regions >10 mm from the clinical tumor boundaries (Table 1: cases 1, 12, 14, 15, 17, and 19).

Molecular risk assessment of low-grade lesions. Because histology is a poor indicator of outcome for margins with little (low-grade) or no histologic change, we used molecular analysis to further define risk for FVL and FVR margins. An example of this combined analysis and its value in assessing FVL margins is shown for case 10 (Fig. 3).

Microsatellite analysis of LOH at 3p, 9p, and 17p was done for 32 biopsies, consisting of all 19 FVL margins showing low-grade dysplasia or no dysplasia, and 13 FVR margin biopsies: the single case with mild dysplasia and 12 randomly chosen cases with no dysplasia (Fig. 2). As shown in Fig. 4A, consistently higher rates of LOH in all categories of comparisons were observed in FVL margins as compared with FVR margins. Such higher rates were significant at 9p (53% versus 8%, $P = 0.01$), for >1 arm lost (37% versus 0%, $P = 0.03$), for LOH at 3p and/or 9p only (63% versus 23%, $P = 0.04$), and for 3p and/or 9p plus 17p (37% versus 0%, $P = 0.03$; Table 2). Strikingly, of the four FVL margins with no dysplasia, two showed LOH at 3p and/or 9p plus 17p, and one showed LOH at 3p (Fig. 2). Of the 13 FVR margins, 3 also showed LOH at 3p and/or 9p, including the single mild dysplasia that was FVR.

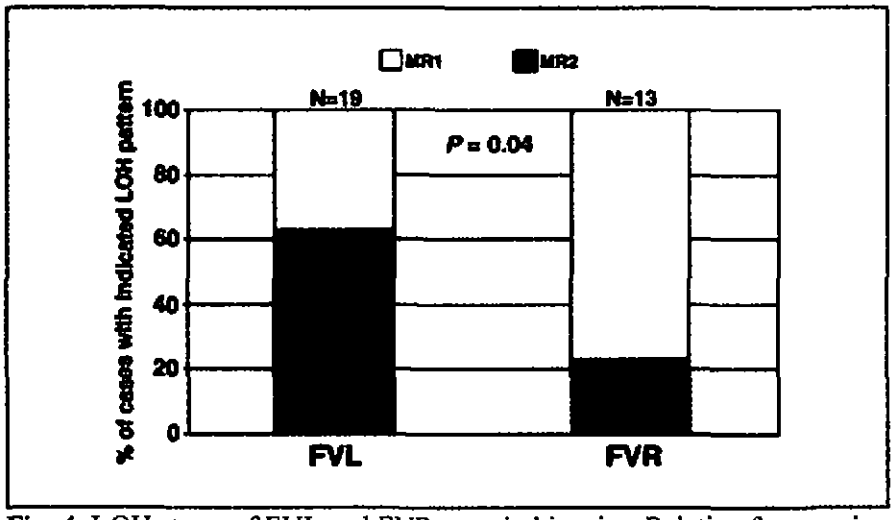


Fig. 4. LOH status of FVL and FVR margin biopsies. Relative frequencies of two molecular patterns previously associated with recurrence (22): MR1, no LOH at 3p and 9p (*open columns*); MR2, LOH at 3p and/or 9p (*solid columns*; see Fig. 2).

	FVL (%)	FVR (%)	*P*
No. of margin biopsies	19	13	
LOH at individual arms			
at 3p	5 of 19 (26)	2 of 13 (15)	0.67
at 9p	10 of 19 (53)	1 of 13 (8)	**0.01**
at 17p	7 of 19 (37)	1 of 13 (8)	0.1
Any loss	12 of 19 (63)	4 of 13 (31)	0.15
>1 loss (as ≥2 loss)	7 of 19 (37)	0 of 13 (0)	**0.03**

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

LOH at 3p and/or 9p	12 of 19 (63)	3 of 13 (23)	**0.04**
LOH at 3p and/or 9p plus 17p	7 of 19 (37)	0 of 13 (0)	**0.03**

Table 2. Frequencies of occurrence of other LOH patterns

As mentioned above, six tumors showed histologic changes of high-grade dysplasia and above in biopsies taken from FVL regions >10 mm from the clinical tumor boundaries. Molecular assessment showed an additional two cases with molecular risk in biopsies taken from FVL regions >10 mm from the clinical tumor boundaries (Table 1, cases 3 and 6).

Discussion

Molecular technology has begun to shed new light on the definition of "field-at-risk" in patients with oral cancer. In this study of fluorescence field changes, we show that the development of new optical techniques that enable us to visualize spectral alterations associated with oral cancer could add a further dimension to these developing paradigms regarding the concept of cancer/risk field.

Our data indicate strongly that the field of FV alterations (FVL) within or beyond the clinically apparent tumor area is associated with morphologic high-grade and molecular high-risk tissue change. All the 20 tumors in this study displayed FVL. All but 1 of the 36 margin biopsies from the subclinical FVL field had either histologic dysplasia/cancer and/or genetic alterations associated with molecular risk. Seventeen of the 36 cases (47%) had cancer or severe dysplasia and 15 cases (42%) had low-grade dysplasia. Nine of the 15 latter cases showed LOH at 3p and/or 9p, a molecular pattern associated with a 26-fold increase in relative cancer risk for tumor recurrence (29). Only 4 of the 36 (11%) FVL margins were not dysplastic; however, three of the four biopsies showed LOH at 3p and/or 9p when assessed molecularly. In contrast, only 1 of the 66 FVR margins was dysplastic (low-grade) and 3 of the 13 FVR margins analyzed for LOH showed molecular risk (includes the dysplastic case).

These findings add to the growing evidence that supports the use of FV to detect cancers and high-risk lesions (16, 30–32), including occult or nonapparent lesions/areas (18). The closest report existing in the literature to our present study is that of Svistun et al. (16) in which the authors evaluate a similar visual analysis system on excised oral cancer tissue and surrounding tissue *ex vivo*. The best subset of the illumination and detection wavelengths found in their study is identical to the ones used by the FV device in the present study. Although they had a small number of cases (four), their limited results indicated a correspondence between pathology and abnormal fluorescence. A limitation of the study, however, was the use of excised tissue and the identification of areas of altered fluorescence by a surgeon using pictures of this tissue under different conditions.

One of the most difficult and contentious issues with respect to treatment of oral cancers involves the decision on the width of clinically normal tissue that should be removed in addition to the tumor. In an effort to remove occult high-risk field change, surgeons frequently remove an arbitrary 10 mm or more of normal-looking mucosal margin when excising oral cancer, if anatomically possible. Unfortunately, this approach still fails to completely remove the occult high-risk field changes in many patients, resulting in a high-rate of tumor recurrence. Our data showed that such occult change is a frequent event (found in 19 of the 20 tumors), and that the width of this subclinical extension varies considerably (4-25 mm), frequently extending in at least one direction by >10 mm (Table 1). If a 10-mm clearance of clinical tumor was used arbitrarily in this sample set, half of the 20 tumors in this study would have cancer or dysplasia at the surgical margin, with six cases (30%) showing severe dysplasia or *CIS*. These six tumors would have a high chance of tumor recurrence because of the inadequate removal.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

The present study is the first description of an FV-characterized field as ascertained directly in a clinical surgical setting. As such, the data represents a new phenotype that could contribute significantly to our concept of cancer/risk field. More research is required to further define it biologically and clinically. In addition to histology, this report has integrated FV status with molecular changes to assess the cancer/risk field. There was a strong association of LOH with FVL; however, this molecular change was also present in 3 of 12 FVR margins. These data illustrate the complexity of the cancer field and support the need for a multiparameter assessment of such change. Optical devices and molecular techniques could complement each other. For example, surgical margins of oral cancer have been examined intraoperatively using quantitative methylation-specific PCR and methylation-positive margins have been identified (33). Optical devices could enhance this molecular mapping. In turn, the assessment of FVL boundaries for such molecular change or others (e.g., *p53* mutation with mutation-specific plaque hybridization assay; ref. 5) would improve our understanding of the nature of this new phenotype. It should be noted that the need for multiparameter assessment of the cancer field also includes the development of new approaches to assessing the depth of cancer extension *in vivo*, as the current device assesses mainly lateral cancer spread.

Finally, our data found no difference between *CIS* and invasive SCC in terms of the FV field expansion. The information is important because the usual recommendation for preinvasive high-grade lesions tend to be more conservative with smaller margins of normal-looking mucosa. The study results suggest that a subgroup of these preinvasive lesions may have extensive lateral fields, some occult, and as such, would require a more aggressive therapy.

In summary, the current study is an important step in the development of a potential integration of optical technology into the management of patients with oral cancer. The device will need to be integrated with information from other sources, both histologic and molecular, and experience with the device will have to be associated with clinical outcome before its clinical value can be established. However, as a proof-of-principle, our data has, for the first time, shown that direct FV can identify subclinical high-risk fields with cancerous and precancerous changes in the operating room setting.

Footnotes

Grant support: R01 DE13124 and R01 DE17013 from the National Institute of Dental and Craniofacial Research and MOP-77663 from the Canadian Institutes of Health Research, and a Clinician Scientist Award from the Canadian Institutes of Health Research (C.F. Poh).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 5/30/06; revised 7/25/06; accepted 8/10/06.

References

1. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963–8.[CrossRef][Medline]
2. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003;63:1727–30.[Abstract/Free Full Text]
3. van Houten VM, Leemans CR, Kummer JA, et al. Molecular diagnosis of surgical margins and local recurrence in head and neck cancer patients: a prospective study. Clin Cancer Res 2004;10:3614–20.[Abstract/Free Full Text]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

4. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994;73:187–90.[CrossRef][Medline]

5. Brennan JA, Mao L, Hruban RH, et al. Molecular assessment of histopathological staging in squamous-cell carcinoma of the head and neck. N Engl J Med 1995;332:429–35.[Abstract/Free Full Text]

6. Hittelman WN, Kim HJ, Lee JS, et al. Detection of chromosome instability of tissue fields at risk: *in situ* hybridization. J Cell Biochem Suppl 1996;25:57–62.[Medline]

7. Tabor MP, Brakenhoff RH, van Houten VM, et al. Persistence of genetically altered fields in head and neck cancer patients: biological and clinical implications. Clin Cancer Res 2001;7:1523–32.[Abstract/Free Full Text]

8. Partridge M, Pateromichelakis S, Phillips E, Emilion GG, A'Hern RP, Langdon JD. A case-control study confirms that microsatellite assay can identify patients at risk of developing oral squamous cell carcinoma within a field of cancerization. Cancer Res 2000;60:3893–8.[Abstract/Free Full Text]

9. Tabor MP, Brakenhoff RH, Ruijter-Schippers HJ, Kummer JA, Leemans CR, Braakhuis BJ. Genetically altered fields as origin of locally recurrent head and neck cancer: a retrospective study. Clin Cancer Res 2004;10:3607–13.[Abstract/Free Full Text]

10. Lam S, MacAulay C, Hung J, LeRiche J, Profio AE, Palcic B. Detection of dysplasia and carcinoma *in situ* with a lung imaging fluorescence endoscope device. J Thorac Cardiovasc Surg 1993;105:1035–40.[Abstract]

11. Ramanujam N, Mitchell MF, Mahadevan A, et al. *In vivo* diagnosis of cervical intraepithelial neoplasia using 337-nm-excited laser-induced fluorescence. Proc Natl Acad Sci U S A 1994;91:10193–7.[Abstract/Free Full Text]

12. Gillenwater A, Jacob R, Ganeshappa R, et al. Noninvasive diagnosis of oral neoplasia based on fluorescence spectroscopy and native tissue autofluorescence. Arch Otolaryngol Head Neck Surg 1998;124:1251–8.[Abstract/Free Full Text]

13. Zhang L, Michelsen C, Cheng X, et al. Molecular analysis of oral lichen planus. A premalignant lesion? Am J Pathol 1997;151:323–7.[Abstract]

14. Schantz SP, Kolli V, Savage HE, et al. *In vivo* native cellular fluorescence and histological characteristics of head and neck cancer. Clin Cancer Res 1998;4:1177–82.[Abstract]

15. Ingrams DR, Dhingra JK, Roy K, et al. Autofluorescence characteristics of oral mucosa. Head Neck 1997;19:27–32.[CrossRef][Medline]

16. Svistun E, Alizadeh-Naderi R, El-Naggar A, Jacob R, Gillenwater A, Richards-Kortum R. Vision enhancement system for detection of oral cavity neoplasia based on autofluorescence. Head Neck 2004;26:205–15.[CrossRef][Medline]

17. Lane PM, Gilhuly T, Whitehead P, et al. Simple device for the direct visualization of oral-cavity tissue fluorescence. J Biomed Opt 2006;11:24006.

18. Poh CF, Ng SP, Williams PM, et al. Direct Fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. Head Neck 2006 Sept. 18 on-line publication.

19. Qu J, MacAulay C, Lam S, Palcic B. Laser induced fluorescence spectroscopy at endoscopy: tissue optics; Monte Carlo modeling and *in vivo* measurements. Optical Eng 1995;34:3334–43.[CrossRef]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

20. Muller MG, Valdez TA, Georgakoudi I, et al. Spectroscopic detection and evaluation of morphologic and biochemical changes in early human oral carcinoma. Cancer 2003;97:1681–92.[CrossRef][Medline]

21. Lippman SM, Lee JJ. Reducing the "risk" of chemoprevention: defining and targeting high risk-2005 AACR Cancer Research and Prevention Foundation Award Lecture. Cancer Res 2006;66:2893–903.[Abstract/Free Full Text]

22. Zhang L, Williams M, Poh CF, et al. Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. Cancer Res 2005;65:8017–21.[Abstract/Free Full Text]

23. Greene FL, Page DL, Fleming ID, et al., editors. AJCC cancer staging manual. 6th ed. New York (NY): Springer; 2002.

24. Mao L. Can molecular assessment improve classification of head and neck premalignancy? Clin Cancer Res 2000;6:321–2.[Free Full Text]

25. Califano J, van der Riet P, Westra W, et al. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res 1996;56:2488–92.[Abstract/Free Full Text]

26. Mao L, Lee JS, Fan YH, et al. Frequent microsatellite alterations at chromosomes 9p21 and 3p14 in oral premalignant lesions and their value in cancer risk assessment. Nat Med 1996;2:682–5.[CrossRef][Medline]

27. Rosin MP, Cheng X, Poh C, et al. Use of allelic loss to predict malignant risk for low-grade oral epithelial dysplasia. Clin Cancer Res 2000;6:357–62.[Abstract/Free Full Text]

28. Lee JJ, Hong WK, Hittelman WN, et al. Predicting cancer development in oral leukoplakia: ten years of translational research. Clin Cancer Res 2000;6:1702–10.[Abstract/Free Full Text]

29. Rosin MP, Lam WL, Poh C, et al. 3p14 and 9p21 loss is a simple tool for predicting second oral malignancy at previously treated oral cancer sites. Cancer Res 2002;62:6447–50.[Abstract/Free Full Text]

30. Betz CS, Mehlmann M, Rick K, et al. Autofluorescence imaging and spectroscopy of normal and malignant mucosa in patients with head and neck cancer. Lasers Surg Med 1999;25:323–34.[CrossRef][Medline]

31. Heintzelman DL, Utzinger U, Fuchs H, et al. Optimal excitation wavelengths for *in vivo* detection of oral neoplasia using fluorescence spectroscopy. Photochem Photobiol 2000;72:103–13.[CrossRef][Medline]

32. Andersson-Engels S, Klinteberg C, Svanberg K, Svanberg S. *In vivo* fluorescence imaging for tissue diagnostics. Phys Med Biol 1997;42:815–24.[CrossRef][Medline]

33. Goldenberg D, Harden S, Masayesva BG, et al. Intraoperative molecular margin analysis in head and neck cancer. Arch Otolaryngol Head Neck Surg 2004;130:39–44.[Abstract/Free Full Text]

Commentary

Fluorescence Visualization in Oral Neoplasia: Shedding Light on an Old Problem

William H. Westra and David Sidransky
Clin. Cancer Res. 2006 12: 6594-6597. [Full Text] [PDF]

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

B4. DentLight 510(k)'s and Product Literature

K101140

510(k) Summary
for
Dentlight Oral Exam Light Kit

JUL 16 2010

1. APPLICANT

DentLight Inc.
1411 E. Campbell Rd., Suite 500
Richardson, TX 75081

Contact Person: Richard Liu
Tel: 972-889-8857
Fax: 972-346-6550

Date Prepared: April 9, 2010

2. DEVICE NAME

Proprietary Name: Dentlight Oral Exam Light Kit

Common/Usual Name: Oral Examination Light

Classification Name: Ultraviolet Detector (872.6350)

3. PREDICATE DEVICES

Velscope (K070523) by LED Medical Diagnostics

Sapphire O/E Oral Examination System by Den-Mat Holdings (K073483)

Identafi 3000 (K090135) by Trimira, Remicalm

4. DEVICE DESCRIPTION

Dentlight Oral Exam Light Kit is a rechargeable-battery-powered cordless unit designed for illumination and examination for dental and physician's office on any procedures which require a small homogenous and well-defined spot and natural tissue reflectance and fluorescence visualization of healthy and abnormal tissue.

Dentlight Oral Exam Light Kit consists of a cordless unit with interchangeable light head (White and Violet), custom adaptable Fluorescence Loupe Filters and Filter Caps, Charging Stand, Power Adapter, and Patient Protective Eyewear Goggle.

5. INTENDED USE

Dentlight Oral Exam Light Kit is indicated for providing illumination to aid visualization during oral procedures and an adjunct to enhance the visualization for oral examination of mucosal abnormalities and oral lesions.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

6. TECHNOLOGICAL CHARACTERISTICS AND SUBSTANDTIAL EQUIVALENCE

Dentlight Oral Exam Light Kit is substantially equivalent to K070523, K073483, and K090135 in intended use and operation; each uses fluorescence and/or reflectance as the primary mode for enhanced visualization of tissue for determining oral tissue abnormalities.

Predicate K070523 uses 120V AC powered metal halide light to produce a single collimated blue light and views fluorescence through a connected handpiece with a filtered lens.

Predicate K073483 uses 120V AC powered Xenon plasma arc light and filters to produce a single collimated blue light and views fluorescence through a connected handpiece with a filtered lens.

Predicate K090135 uses AA-battery-powered low power LED light to produce a violet light at near site to tissue and view fluorescence through a broadband polarized filter glass. A selectable wavelength mechanism is built in with additional white and amber LED lights that compliment fluorescence image.

Dentlight Oral Exam Light Kit offers two illumination modalities and one common detection/viewing mechanism. Both illumination modalities use LED light source in multiple wavelength spectra as illumination or excitation source for tissue fluorescence/reflection. The operational principles of the proposed and predicate devices are identical with the primary mode for enhanced visualization of tissue through fluorescence. The operator chooses the appropriate wavelength light source to illuminate regions of oral cavity for inspection.

The major differences between the proposed Dentlight Oral Exam Light Kit and the predicate devices are the magnified high contrast filter used in the detection/viewing, the illumination intensity, size, weight and portability of the device. The increased light intensity of the proposed Dentlight Oral Exam Light Kit using high power LED allows the illumination and excitation with improved clarity. The improved portability with cordless hands free operation or wand operation enables better, easier and faster exam procedures. The size and weight is a benefit to constant patient operations and counter space.

7. PERFORMANCE TESTING AND COMPLIANCE

The following testing was conducted to evaluate the functionality and performance of the proposed Dentlight Oral Exam Light Kit:

- Optical Power Testing
- Optical wavelength
- Beam Quality
- Illumination and Fluorescence Image

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

The Dentlight Oral Exam Light Kit is designed to comply with electrical safety and electromagnetic compatibility and will comply with electrical safety requirement established by IEC 60601-1-2.

We believe the similarity of the Dentlight Oral Exam Light Kit to the legally marketed predicate devices and the performance data provided support the safety and effectiveness of the Dentlight Oral Exam Light Kit for the indicated use.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room –WO66-G609
Silver Spring, MD 20993-0002

Dr. Richard Liu
President
DentLight, Incorporated
1411 East Campbell Road, Suite 500
Richardson, Texas 75081

JUL 16 2010

Re: K101140
Trade/Device Name: DentLight Oral Exam Light Kit
Regulation Number: 21 CFR 872.6350
Regulation Name: Ultraviolet Detector
Regulatory Class: II
Product Code: EAQ, NXV
Dated: April 9, 2010
Received: April 22, 2010

Dear Dr. Liu

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please go to http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHOffices/ucm115809.htm for the Center for Devices and Radiological Health's (CDRH's) Office of Compliance. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

for

Anthony D. Watson, B.S., M.S., M.B.A.
Director
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Indications for Use

510(k) Number (if known): K101140

Device Name: Dentlight Oral Exam Light Kit

Indications For Use:

Dentlight Oral Exam Light Kit is indicated to be used by a dentist and physician for illumination to aid visualization during oral procedures and as an adjunct to enhance the visualization for oral examination of mucosal abnormalities and oral lesions.

Prescription Use X (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

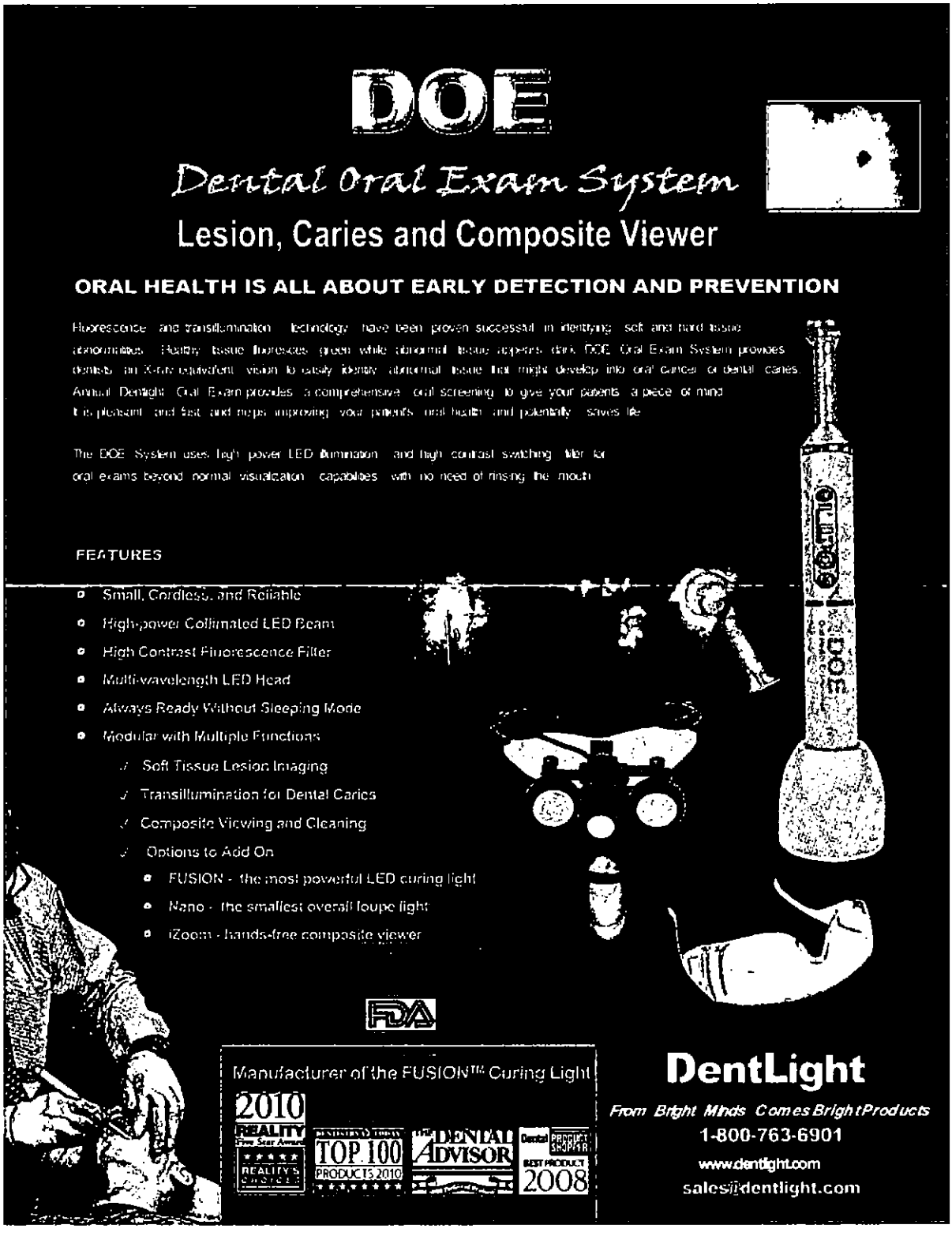
Concurrence of CDRH, Office of Device Evaluation (ODE)

BBetz DDS for Dr. Susan Runner
(Division Sign-Off)
Division of Anesthesiology, General Hospital
Infection Control, Dental Devices

510(k) Number: K101140

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

B5. DentLight Marketing Materials



FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

DentLight DOE

High Power LED and High Contrast Fluorescence Filter

Pushing the technology envelopes, DOE uses high power LED illumination and high contrast magnified switching filter for oral exams beyond normal visualization capabilities.

Multi-wavelength and Interchangeable LED

Easily interchangeable LED head design enables multi-wavelength oral exam with white and violet light for best early determination of normal and malignant tissues and oral lesions.

Collimated Beam

Patent-pending collimated and uniform beam enables best illumination and excitation of fluorescence to avoid visual artifacts.

Constant Power

With unique heat sink technology and constant current LED driver, DOE maintains constant power throughout the battery run time allowing 20 patients exams in one full charge.

Small, Portable and Reliable

At the size of a normal handpiece, fully portable with smart non-memory rechargeable battery, plug-start power driver, and shock-proof durability with solid metal construction, DOE works any time the doctors need it.

Integration with Loupes and Recording Camera

DOE comes with patent-pending integrated loupe filters and is compatible with major loupes and digital cameras making it easily integrated with standard practice for oral exam and record keeping. Best of all, you can easily convert it into the most powerful LED curing light - FUSION.

Weight	110 grams (handpiece)
Diameter	22 mm
Wavelength	6000 K (white)
	410 nm (Violet)
Battery Run Time	40 min
Recharging Time	90 min

White Light Violet Light

Order information

7700010 DOE Kit
Including DOE Wand with Violet and White Light Head, Universal 2.5x Flip-up Loupes, Fluorescence Filter Pairs, Charging Stand, Charge Adapter, Two Exam Tips, Patient Eyewear Goggle, and 100 barrier sleeves.

7701010 DOE Silver Kit
Including DOE Wand with Violet Light Head, Fluorescence Filter Pairs, Nano Loupe Light, Charging Stand, Charge Adapter, Patient Eyewear Goggle, and 100 barrier sleeves.

7500100 FUSION to DOE Upgrade Kit
7500101 DOE Starter Kit
7701100 58mm SLR Camera Filter
7701200 43mm Point and Shoot Digital Camera Filter
7701300 37mm Point and Shoot Digital Camera Filter

DentLight, Inc • 1411 E. Campbell Rd., Ste 500 • Richardson TX 75081 • 800.763.6901 • Fax 972.346.6550
sales@dentlight.com • www.dentlight.com

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

YOUR PATIENT'S ORAL HEALTH IS YOUR MAIN CONCERN.

The Solution: DOE™ Oral Exam System by DentLight!

ORAL HEALTH IS ALL ABOUT EARLY DETECTION AND PREVENTION

Fluorescence and tissue reflectance technology have been proven successful in identifying soft tissue abnormalities. Healthy tissue fluoresces green. DOE Oral Exam System by DentLight pushes the technology envelope in helping dentists or hygienists to easily identify abnormal tissue that might develop into oral cancer at an affordable price. Annual DentLight Oral Exam provides a comprehensive oral screening to give your patients a piece of mind. It is pleasant and fast, and could help save your patient's life

The DOE System uses high power LED illumination and high contrast switching filter for oral exams beyond normal visualization capabilities.

FEATURES

- Small, Cordless, and Reliable
- High-power Collimated LED Beam
- High Contrast Fluorescence Filter
- Multi-wavelength and Interchangeable LED
- Always ready without sleeping mode
- Modular with Multiple Functions
  - Transillumination for dental caries and cracks
  - Options to upgrade to FUSION - the most powerful LED curing light
  - Composite viewing and cleaning
- Priced under $2,000

DentLight Oral Health Examination System contains:
Cordless DentLight Oral Exam Wand with interchangeable violet and white light heads, Universal 2.5x flip-up loupes with fluorescence filter, charging stand, charger adapter, patient protective eyewear, and 100 Barrier Sleeves.

Manufacturer of the FUSION™ Curing Light

2010 REALITY Five Star Award REALITY'S CHOICE | TOP 100 PRODUCTS 2010 | THE DENTAL ADVISOR | Dental PRODUCT SHOPPER BEST PRODUCT 2008

DentLight
From Bright Minds Comes Bright Products™
800.763.6901
www.dentlight.com
sales@dentlight.com

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

DentLight™

Violet Light

White Light

Oral health is all about early detection and prevention. Fluorescence and tissue reflectance technology have been proven successful in identifying soft tissue abnormalities. Healthy tissue fluoresces green. DOE Oral Exam System by DentLight pushes the technology envelope in helping dentists or hygienists to easily identify abnormal tissue that might develop into oral cancer at an affordable price. Annual Dentlight Oral Exam provides a comprehensive oral screening to give your patients a piece of mind. It is pleasant and fast, and could help save your patient's life.
The DOE System uses high power LED illumination and high contrast switching filter for oral exams beyond normal visualization capabilities.

High-power LED and High Contrast Fluorescence Filter
Pushing the technology envelopes, Dentlight Oral Exam Light uses high power LED illumination and high contrast switching filter for oral exams beyond normal visualization capabilities.

Multi-wavelength and Interchangeable LED
Easily interchangeable LED head design enables multi-wavelength oral exam with white and violet light for best early determination of normal and malignant tissues and oral lesions.

Collimated Beam
Patent-pending collimated and uniform beam enables best illumination and excitation of fluorescence to avoid visual artifacts.

Constant Power
With unique heat sink technology and constant current LED driver, Dentlight Oral Exam Light maintains constant power throughout the battery run time allowing 20 patient exams in one full charge.

Small, Portable and Reliable
At the size of a normal handpiece, fully portable and with smart non-memory rechargeable battery, cooling design, and plug-start power driver, Dentlight Oral Exam Light works any time the doctors need it.

Integration and Multiple Functions
Dentlight Oral Exam Light comes with patent-pending integrated loupe filters and is compatible with digital cameras making it easily integrated with standard practice for oral exam and record keeping. Best of all, you can easily convert it into the most powerful LED curing light - FUSION.

DentLight, Inc • 1411 East Campbell Rd, Ste 500 • Richardson, TX 75081 • 800.763.6901 • Fax 972.346.6550
sales@dentlight.com • www.dentlight.com

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

C. Abstracts supporting Indications for Use and Marketing Claims and Bibliography

Selected Publications and Abstracts were selected from PubMed Search for:

Disease State:
Oral Cancer + Screening yielded 34100 articles
Oral Cancer + Detection yielded 2177 articles

Technology and Disease State:
Fluorescence + Oral Cancer yielded 607 articles

Understanding the Biological Basis of Autofluorescence Imaging for Oral Cancer Detection: High-Resolution Fluorescence Microscopy in Viable Tissue

Ina Pavlova[1], Michelle Williams[2], Adel El-Naggar[2], Rebecca Richards-Kortum[4] and Ann Gillenwater[3]

Authors' Affiliations: [1] Department of Biomedical Engineering, The University of Texas at Austin, Austin, Texas; [2] Pathology and [3] Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center; and [4] Department of Bioengineering, Rice University, Houston, Texas

Requests for reprints: Ann Gillenwater, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Unit 441, Houston, TX 77030. Phone: 713-792-8841; Fax: 713-794-4662; E-mail: agillenw@mdanderson.org .

Purpose: Autofluorescence imaging is increasingly used to noninvasively identify neoplastic oral cavity lesions. Improving the diagnostic accuracy of these techniques requires a better understanding of the biological basis for optical changes associated with neoplastic transformation in oral tissue.

Experimental Design: A total of 49 oral biopsies were considered in this study. The autofluorescence patterns of viable normal, benign, and neoplastic oral tissue were imaged using high-resolution confocal fluorescence microscopy.

Results: The autofluorescence properties of oral tissue vary significantly based on anatomic site and pathologic diagnosis. In normal oral tissue, most of the epithelial autofluorescence originates from the cytoplasm of cells in the basal and intermediate regions, whereas structural fibers are responsible for most of the stromal fluorescence. A strongly fluorescent superficial layer was observed in tissues from the palate and the gingiva, which contrasts with the weakly fluorescent superficial layer found in other oral sites. Upon UV excitation, benign inflammation shows decreased epithelial fluorescence, whereas dysplasia displays increased epithelial fluorescence compared with normal oral tissue. Stromal fluorescence in both benign inflammation and dysplasia drops significantly at UV and 488 nm excitation.

Conclusion: Imaging oral lesions with optical devices/probes that sample mostly stromal fluorescence may result in a similar loss of fluorescence intensity and may fail to distinguish benign from precancerous lesions. Improved diagnostic accuracy may be achieved by designing optical probes/devices that distinguish epithelial fluorescence from stromal fluorescence and by using excitation wavelengths in the UV range.

Clinical Cancer Research 14, 2396-2404, April 15, 2008. doi: 10.1158/1078-0432.CCR-07-1609

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Spectroscopic diagnosis and imaging of invisible pre-cancer.

Badizadegan K, Backman V, Boone CW, Crum CP, Dasari RR, Georgakoudi I, Keefe K, Munger K, Shapshay SM, Sheetse EE, Feld MS.

Massachusetts Institute of Technology Laser Biomedical Research Center, USA.

The theme of this paper is the use of optical spectroscopy to diagnose invisible pre-cancer in patients undergoing endoscopy and similar medical procedures. We describe three techniques that provide diagnostic information and two instruments to implement them, the FastEEM for studying small regions of tissue and the LSS (light scattering spectroscopy) imaging system for wide-area surveillance. The FastEEM is an optical fiber clinical device that collects spectra of reflected light and fluorescence at multiple excitation wavelengths from the tissue, all in a fraction of a second. Quantitative information is obtained in real time, without removing the tissue and without the need for staining and fixation. Three types of spectral information are extracted intrinsic fluorescence, diffuse reflectance and elastic light scattering. Each of the three analyses is based on a biophysical model, and each provides complementary quantitative physical and chemical information about cellular/tissue structures. This information is used to make a combined spectral diagnosis, a method we call tri-modal spectroscopy (TMS). Promising clinical studies are being carried out on patients undergoing routine pre-cancer surveillance in the oral cavity, the uterine cervix and the gastrointestinal tract. The LSS imaging system provides wide-area spectroscopic images of the epithelium, typically 2 cm in each dimension, depicting the size distribution and chromatin content of the cell nuclei, which are key parameters in diagnosing pre-cancer. This instrument is in preclinical stages of development, although a laboratory prototype has been used to create diagnostic images in resected colon polyp samples. The combination of the TMS/FastEEM and LSS imaging instrument will constitute a powerful new diagnostic tool, with LSS imaging to provide wide area surveillance and the TMS probe to provide detailed information on suspect tissue sites.

PMID: 14992412 [PubMed - indexed for MEDLINE]

Optimal visual perception and detection of oral cavity neoplasia

Utzinger, U. Bueeler, M. Sanghoon Oh Heintzelman, D.L. Svistun, E.S. Abd-El-Barr, M. Gillenwater, A. Richards-Kortum, R.
Dept. of Biomed. Eng. & Obstetrics & Gynecology, Univ. of Arizona, Tucson, AZ, USA;

This paper appears in: **Biomedical Engineering, IEEE Transactions on**
Publication Date: Mar 2003 Volume: 50, Issue: 3 On page(s): 396- 399
ISSN: 0018-9294 INSPEC Accession Number: 7550856
Digital Object Identifier: 10.1109/TBME.2003.808832
Posted online: 2003-03-20 11:22:39.0

Abstract
The most common way to detect disease is by visual inspection of the suspect tissue. However, the human eye is not optimized for this task because the perceived spectrum of light is divided into three channels, all of which have overlapping spectral sensitivity curves. Here, we present new methods to optimize visually perceived contrast based on spectral differences between normal and abnormal tissue. We apply these methods to the perception of fluorescence emission from the oral cavity. Abnormalities in the oral cavity are optimally perceived when the excitation is between **420-440 nm**. To optimally visualize fluorescence at 340-nm excitation, the emission should be observed through a blue bandpass filter transmitting light at 430 nm.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Vision enhancement system for detection of oral cavity neoplasia based on autofluorescence

Ekaterina Svistun, MS[1], Reza Alizadeh-Naderi, BS[2], Adel El-Naggar, MD, PhD[2], Rhonda Jacob, DDS[2], Ann Gillenwater, MD[2], Rebecca Richards-Kortum, PhD[1*]

[1]Department of Biomedical Engineering, The University of Texas at Austin, Austin, Texas 78712
[2]Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

email: Rebecca Richards-Kortum (kortum@mail.utexas.edu)

*Correspondence to Rebecca Richards-Kortum,

ABSTRACT

Background.

Early detection of squamous cell carcinoma (SCC) in the oral cavity can improve survival. It is often difficult to distinguish neoplastic and benign lesions with standard white light illumination. We evaluated whether a technique that capitalizes on an alternative source of contrast, tissue autofluorescence, improves visual examination.

Methods.

Autofluorescence of freshly resected oral tissue was observed visually and photographed at specific excitation/emission wavelength combinations optimized for response of the human visual system and tissue fluorescence properties. Perceived tumor margins were indicated for each wavelength combination. Punch biopsies were obtained from several sites from each specimen. Sensitivity and specificity were evaluated by correlating histopathologic diagnosis with visual impression.

Results.

Best results were achieved with illumination at 400 nm and observation at 530 nm. Here, sensitivity and specificity were 91% and 86% in discrimination of normal tissue from neoplasia. This compares favorably with white light examination, in which sensitivity and specificity were 75% and 43%.

Conclusions.

Oral cavity autofluorescence can be easily viewed by the human eye in real time. Visual examination of autofluorescence enhances perceived contrast between normal and neoplastic oral mucosa in fresh tissue resections. *Head Neck* **26:** 205-215, 2004

Autofluorescence characteristics of oral mucosa

Duncan R. Ingrams, FRCS[1], Jagdish K. Dhingra, FRCS[1], Krishnendu Roy, BTech[1,2], Donald F. Perrault Jr, BS[1], Ian D. Bottrill, FRCS[1], Sadru Kabani, DMD[3], Elie E. Rebeiz, MD[1], Michail M. Pankratov, MS[1], Stanley M. Shapshay, MD[1*], Ramasamy Manoharan, PhD[4], Irving Itzkan, PhD[4], Michael S. Feld, PhD

[1]Otolaryngology Research Center for Advanced Endoscopic Applications, New England Medical Center, Tufts University School of Medicine, 750 Washington Street, NEMC 187, Boston, MA 02111
[2]Department of Biomedical Engineering, Boston University, Boston, Massachusetts
[3]Department of Oral Pathology, Tufts University School of Dental Medicine, Boston, Massachusetts
[4]George R. Harrison Spectroscopy Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

*Correspondence to Stanley M. Shapshay, Otolaryngology Research Center for Advanced Endoscopic Applications, New England Medical Center, Tufts University School of Medicine, 750 Washington Street, NEMC 187, Boston, MA 02111

ABSTRACT

Background

The fluorescence characteristics of tissues depend upon their biochemical composition and histomorphological architecture, both of which undergo a change during malignant transformation. These changes are detectable as an alteration in the fluorescence spectral profile of the tissues.

Methods

Biopsy specimens from clinically suspicious lesions and normal-appearing oral mucosa were obtained from patients. Fluorescence spectroscopic measurements were obtained to study the differences between normal and dysplastic tissues and to determine the most appropriate excitation wavelength(s) for exploiting these differences.

Results

Fluorescence spectra from a total of 12 histologically normal (healthy mucosa or benign lesions) and ten abnormal (dysplastic or malignant) tissue samples were compared. Significant spectral differences were seen between the two groups. These differences were most marked at the excitation wavelength of 410 nm. Using this wavelength, fluorescence correctly diagnosed 20 of 22 samples studied.

Conclusions

This technique accurately differentiates normal from abnormal tissues in vitro and has the potential applications for in vivo use as a noninvasive diagnostic tool. © 1997 John Wiley & Sons, Inc. Head Neck **19**: 27-32, 1997.

Autofluorescence imaging and spectroscopy of normal and malignant mucosa in patients with head and neck cancer

C.S. Betz[1], M. Mehlmann, Dipl. Ing.[2], K. Rick, PhD[2], H. Stepp, PhD[2], G. Grevers, MD[1], R. Baumgartner, PhD[2], A. Leunig, MD[1]

[1]Department of Oto-Rhino-Laryngology/Head & Neck Surgery, Ludwig Maximilian University, 81377 Munich, Germany
[2]Laser-Research Laboratory at the Department of Urology, Ludwig Maximilian University, 81377 Munich, Germany

email: A. Leunig (Andreas.Leunig@hno.med.uni-muenchen.de)

*Correspondence to A. Leunig, Department of Otorhinolaryngology/Head & Neck Surgery, University of Munich, Klinikum Großhadern, Marchioninistr.15, 81377 München, Germany

Abstract

Background and Objective

An early detection of oral cancer might improve the patient's prognosis. We present preliminary results of autofluorescence photodetection of cancerous oral mucosa.

Materials and Methods

49 patients were investigated altogether. In 30 patients, malignant and healthy oral mucosa were excited with violet light (λ = 375 to 440 nm). Images were recorded by a sensitive CCD camera.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Spectrophotometric analysis in the green spectral range was performed on tumorous and innocuous mucosa in 36 patients.

Results

In 13 patients (43.3%), tumors were subjectively better distinguishable from their surroundings through a reduction of green autofluorescence than by ordinary inspection. Tumor detection abilities varied for different locations and tumor morphologies. Spectral analysis showed contrasts in autofluorescence intensities between tumor and normal tissues in 34 patients (94.4%). Autofluorescence spectra of normal mucosa varied both inter- and intraindividually.

Conclusions

Using violet excitation light, camera-based autofluorescence photodetection in the green spectral range presented a highly promising tool for the diagnosis of oral malignomas in almost half of the cases examined. The possible ways on how the obtained results could serve to find a more advanced method for a precise tumor detection in the oral cavity are being discussed. Lasers Surg. Med. 25:323-334, 1999. © 1999 Wiley-Liss, Inc.

Fluorescence photography as a diagnostic method for oral cancer

Kojiro Onizawa[a], Hideo Saginoya[b], Yasunobu Furuya[c] and Hiroshi Yoshida[a]

[a] Department of Oral and Maxillofacial Surgery, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba-shi, Ibaraki-ken 305, Japan

[b] Division of Photographic Studio, University of Tsukuba Hospital, Tsukuba-shi, Ibaraki-ken 305, Japan

[c] Division of Oral and Maxillofacial Surgery, University of Tsukuba Hospital, Tsukuba-shi, Ibaraki-ken 305, Japan

Received 31 May 1996; Revised 11 July 1996; accepted 12 July 1996. Available online 12 December 1997. *Cancer Lett 1996; 108(1): 61–66*

Abstract

This study was carried out to evaluate the diagnostic utility of autofluorescence photography for oral mucosal lesions. The materials consisted of 15 chemically-induced lesions containing carcinomas in 15 hamsters, and 32 oral lesions in 30 patients. In the animal models, orange fluorescence was detected in all squamous cell carcinomas invading the muscle layer, and the intensity of the fluorescence increased with the progress of the lesions. In the clinical application, orange fluorescence was detected in 14 of 16 malignant tumors and in one of 16 benign lesions. These results suggest that fluorescence photography may be useful for the diagnosis of oral cancer, particularly for squamous cell carcinoma

Clinical study for classification of benign, dysplastic, and malignant oral lesions using autofluorescence spectroscopy.

de Veld DC, Skurichina M, Witjes MJ, Duin RP, Sterenborg HJ, Roodenburg JL.

University Hospital Groningen, Department of Oral and Maxillofacial Surgery, Division of Oncology, Groningen 9700 RB, The Netherlands.

Autofluorescence spectroscopy shows promising results for detection and staging of oral (pre-) malignancies. To improve staging reliability, we develop and compare algorithms for lesion classification. Furthermore, we examine the potential for detecting invisible tissue alterations.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Autofluorescence spectra are recorded at six excitation wavelengths from 172 benign, dysplastic, and cancerous lesions and from 97 healthy volunteers. We apply principal components analysis (PCA), artificial neural networks, and red/green intensity ratio's to separate benign from (pre-) malignant lesions, using four normalization techniques. To assess the potential for detecting invisible tissue alterations, we compare PC scores of healthy mucosa and surroundings/contralateral positions of lesions. The spectra show large variations in shape and intensity within each lesion group. Intensities and PC score distributions demonstrate large overlap between benign and (pre-) malignant lesions. The receiver-operator characteristic areas under the curve (ROC-AUCs) for distinguishing cancerous from healthy tissue are excellent (0.90 to 0.97). However, the ROC-AUCs are too low for classification of benign versus (pre-) malignant mucosa for all methods (0.50 to 0.70). Some statistically significant differences between surrounding/contralateral tissues of benign and healthy tissue and of (pre-) malignant lesions are observed. We can successfully separate healthy mucosa from cancers (ROC-AUC>0.9). However, autofluorescence spectroscopy is not able to distinguish benign from visible (pre-) malignant lesions using our methods (ROC-AUC<0.65). The observed significant differences between healthy tissue and surroundings/contralateral positions of lesions might be useful for invisible tissue alteration detection. (c) 2004 Society of Photo-Optical Instrumentation Engineers.

PMID: 15447015 [PubMed - indexed for MEDLINE]

Spectroscopic detection and evaluation of morphologic and biochemical changes in early human oral carcinoma.

Müller MG, **Valdez TA**, **Georgakoudi I**, **Backman V**, **Fuentes C**, **Kabani S**, **Laver N**, **Wang Z**, **Boone CW**, **Dasari RR**, **Shapshay SM**, **Feld MS**.

G. R. Harrison Spectroscopy Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA.

BACKGROUND: Understanding the development and progression of head and neck squamous cell carcinoma is key in the quest for the early diagnosis and prevention of this type of malignancy. The current study correlated early biochemical and histologic changes in oral tissue with spectral features in fluorescence, reflectance, and light scattering spectra acquired in vivo to diagnose early stages of oral malignancies.

METHODS: A total of 91 tissue sites from 15 patients with varying degrees of malignancy (normal, dysplastic, and cancerous sites) and 8 healthy volunteers were analyzed with 3 spectroscopic techniques. Direct biochemical information regarding oral tissue native fluorophores was obtained with intrinsic fluorescence spectroscopy by fitting a linear combination of collagen and the reduced form of nicotinamide adenine dinucleotide (NADH) fluorescence spectra to the intrinsic tissue fluorescence spectra excited with 337 nanometer (nm) and 358-nm laser light. Diffuse reflectance spectroscopy was used to provide information regarding tissue absorption and structure, such as hemoglobin concentration and stroma density, by measuring the wavelength-dependent absorption and scattering coefficients. By subtracting the diffusely reflected component from the measured reflectance, light scattering spectroscopy (LSS) information resulting from single backscattering from epithelial cell nuclei was obtained. LSS provides information concerning the size distribution of cell nuclei.

RESULTS: These optically extracted tissue parameters provide biochemical or structural information in vivo without the need for tissue excision, and can be used to diagnose tissue abnormalities. By combining the information provided by the three techniques, a method known as trimodal spectroscopy, a sensitivity and specificity of 96% and 96%, respectively, in distinguishing cancerous/dysplastic (mild, moderate, and severe) from normal tissue was achieved. In addition, the

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

authors were able to distinguish dysplastic from cancerous tissue with a sensitivity of 64% and a specificity of 90%.

CONCLUSIONS: The results of the current study demonstrated that Trimodal spectroscopy is a highly sensitive and specific technique with which to diagnose tissue abnormalities. Copyright 2003 American Cancer Society.DOI 10.1002/cncr.11255

PMID: 12655525 [PubMed - indexed for MEDLINE]

Fluorescence Visualization Detection of Field Alterations in Tumor Margins of Oral Cancer Patients

Catherine F. Poh[1,2,3], Lewei Zhang[1], Don W. Anderson[5], J. Scott Durham[5], P. Michele Williams[1,3], Robert W. Priddy[1], Ken W. Berean[6], Samson Ng[1], Olivia L. Tseng[7], Calum MacAulay[4] and Miriam P. Rosin[2,7]

Authors' Affiliations: [1] Faculty of Dentistry, University of British Columbia, Departments of [2] Cancer Control Research, [3] Oral Oncology, and [4] Cancer Imaging, British Columbia Cancer Agency, Departments of [5] Surgery (Otolaryngology) and [6] Pathology, Vancouver General Hospital, Vancouver, British Columbia, Canada, and [7] School of Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada

Requests for reprints: Miriam P. Rosin, BC Oral Cancer Prevention Program, BC Cancer Agency/Cancer Control Research Centre, 675 West 10th Avenue, Vancouver, British Columbia, Canada V5Z 1L3. Phone: 604-675-8078; Fax: 604-675-8180; E-mail: Miriam_Rosin@shaw.ca .

Abstract

Purpose: Genetically altered cells could become widespread across the epithelium of patients with oral cancer, often in clinically and histologically normal tissue, and contribute to recurrent disease. Molecular approaches have begun to yield information on cancer/risk fields; tissue optics could further extend our understanding of alteration to phenotype as a result of molecular change.

Experimental Design: We used a simple hand-held device in the operating room to directly visualize subclinical field changes around oral cancers, documenting alteration to fluorescence. A total of 122 oral mucosa biopsies were obtained from 20 surgical specimens with each biopsy being assessed for location, fluorescence visualization (FV) status, histology, and loss of heterozygosity (LOH; 10 markers on three regions: 3p14, 9p21, and 17p13).

Results: All tumors showed FV loss (FVL). For 19 of the 20 tumors, the loss extended in at least one direction beyond the clinically visible tumor, with the extension varying from 4 to 25 mm. Thirty-two of 36 FVL biopsies showed histologic change (including 7 squamous cell carcinoma/carcinomas *in situ*, 10 severe dysplasias, and 15 mild/moderate dysplasias) compared with 1 of the 66 FV retained (FVR) biopsies. Molecular analysis on margins with low-grade or no dysplasia showed a significant association of LOH in FVL biopsies, with LOH at 3p and/or 9p (previously associated with local tumor recurrence) present in 12 of 19 FVL biopsies compared with 3 of 13 FVR biopsies ($P = 0.04$).

Conclusions: These data have, for the first time, shown that direct FV can identify subclinical high-risk fields with cancerous and precancerous changes in the operating room setting.

Clinical Cancer Research Vol. 12, 6716-6722, November 15, 2006

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Complete Articles:

Noninvasive Diagnosis of Oral Neoplasia Based on Fluorescence Spectroscopy and Native Tissue Autofluorescence

Ann Gillenwater, MD; Rhonda Jacob, DDS, MS; Ravi Ganeshappa, MD; Bonnie Kemp, MD; Adel K. El-Naggar, MD, PhD; J. Lynn Palmer, PhD; Gary Clayman, MD, DDS; Michele Follen Mitchell, MD; Rebecca Richards-Kortum, PhD

Arch Otolaryngol Head Neck Surg. 1998;124:1251-1258.

ABSTRACT

Objective To evaluate the clinical potential of fluorescence spectroscopy (a noninvasive technique for assessing the chemical and morphologic composition of tissue) for in vivo detection of oral cavity neoplasia.

Design A fluorescence spectroscopy system recorded spectra from oral cavity sites in 8 healthy volunteers and in 15 patients with premalignant or malignant oral cavity lesions at 337-, 365-, and 410-nm excitation wavelengths in the emission range of 350 to 700 nm. Fluorescence peak intensities and spectral line shapes were compared and diagnostic algorithms were developed to distinguish normal sites from abnormal sites.

Setting The head and neck cancer clinic at a tertiary referral center in Houston, Tex.

Results Differences were found in spectra from normal, dysplastic, and malignant oral mucosa. The fluorescence intensity of normal mucosa was greater than that of abnormal areas. In addition, the ratio of red region (635-nm) to blue region (455-490-nm) intensities was greater in abnormal areas. Diagnostic discrimination was achieved when test site spectra were compared with spectra from a normal site in the same patient. One diagnostic algorithm based on spectra at 337 nm gave a sensitivity of 88% and a specificity of 100%.

Conclusions Consistent differences exist between the fluorescence spectra of abnormal and normal oral mucosa. Therefore, fluorescence spectroscopy has the potential to improve the noninvasive diagnosis of oral cavity neoplasia. Further studies will better define the role of this technique in the detection of premalignant and early oral cancer lesions.

INTRODUCTION

PATIENTS WITH cancer of the oral cavity usually present when their disease is already advanced. Treatment for these patients vs those with early-stage disease is more disfiguring and debilitating, more expensive, and less successful. Early detection of neoplastic changes in the oral cavity has great potential for improving the quality of life and survival rates for patients. The goal of this study was to evaluate the clinical applicability of fluorescence spectroscopy (a noninvasive technique for assessing the chemical and morphologic composition of tissue) for the in vivo detection of oral cavity neoplasia.

Because of the accessibility of the oral cavity to examination and the fairly well-defined risk factors for malignancy, this area should be an ideal location to target for early cancer detection and prevention. The detection of oral cancer, however, relies heavily on clinical experience in recognizing suspicious lesions during physical examination. Detecting premalignant and early malignant lesions, and distinguishing them from more common benign inflammatory conditions, can be extremely difficult, even for experienced practitioners.

Several studies[1-3] have assessed the ability of vital staining with agents such as toluidine blue and Lugol iodine solution to improve diagnostic accuracy of clinical examinations. Although the

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

sensitivity of application of these dyes was 90% or greater in many of these trials, specificity was lower. Most of these studies were conducted by clinicians who were experts in the diagnosis of malignant lesions in the oral cavity, and their results may not reflect the diagnostic predictability of these agents when used by less experienced personnel.

Current clinical practice requires an invasive biopsy with histological examination of abnormally appearing tissue to determine malignant potential. Practitioners and patients, however, are often reluctant to proceed with invasive biopsies of small, asymptomatic oral lesions. The development of a noninvasive and accurate method for real-time screening and diagnosis of oral lesions would have great potential for improving early detection of neoplastic changes, thereby improving the quality of life and survival rates for persons developing squamous cell carcinoma of the oral cavity.

Fluorescence spectroscopy is a new diagnostic modality with the potential to bridge this gap between clinical examination and invasive biopsy. Tissue architecture and biochemical composition can be evaluated in near real time using optical spectroscopy. By scanning the tissue with a small, flexible, fiberoptic probe, subtle alterations induced by dysplasia or inflammation can be detected noninvasively.4 This is accomplished by analyzing the spectrum of the fluorescence emitted by the tissue. The development of software algorithms should allow automated data analysis of various types of spectra to provide instantaneous tissue diagnosis.

Studies of fluorescence spectroscopy for the diagnosis of neoplastic changes have been conducted in a variety of sites, including the gastrointestinal tract,4 cervix,5-6 lung,7 and breast tissue.8 Relatively fewer studies have been conducted on the oral mucosa.9-11 Previously, we evaluated fluorescence spectra in vitro from specimens of head and neck squamous cell carcinoma over a broad spectrum of wavelengths. We found that the excitation wavelengths of 337, 365, and 410 nm produced the greatest separation between normal and abnormal spectra (data not shown). Results of a similar in vitro investigation by Dhingra et al10 showed the greatest differences between normal and abnormal tissue samples at the 410-nm excitation wavelength. In the present study, we characterized fluorescence emission spectra obtained at 3 excitation wavelengths (337, 365, and 410 nm) from clinically normal, dysplastic, and cancerous oral mucosa and assessed the ability to discriminate between normal and abnormal sites by spectral alteration.

PARTICIPANTS AND METHODS

STUDY PARTICIPANTS

Eight healthy volunteers and 15 patients with a known or suspected premalignant or malignant oral cavity lesion were recruited at the Department of Head and Neck Surgery at The University of Texas M. D. Anderson Cancer Center, Houston. The study was reviewed and approved by the Internal Review Board of The University of Texas at Austin and by the Surveillance Committee at M. D. Anderson Cancer Center. Informed consent was obtained from each person in the study.

INSTRUMENTS

The spectroscopic system, as previously described,5-6 incorporates a fiberoptic probe, 2 nitrogen-pumped dye lasers, and an optical multichannel analyzer. The probe consists of a central fiber surrounded by 6 fibers. Three fibers deliver excitation light at wavelengths of 337, 365, and 410 nm. Results of our in vitro analysis of head and neck squamous cell carcinoma specimens suggested that these wavelengths would produce the greatest discrimination between normal and abnormal tissue. The other 4 fibers collect the fluorescence emitted from the tissue. The probe illuminates a 1-mm-diameter spot on the tissue surface, and a quartz shield at the tip of the probe maintains a fixed distance between the fibers and the tissue. The laser has a 5-nanosecond pulse duration and a repetition rate of 30 Hz. The average transmitted pulse energies at 337, 365, and 410 nm were 15.2, 3.3, and 17.4 μJ, respectively.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

The light from the 4 emission-collection fibers is sent to a polychromator, which disperses the light onto an array of diodes. The diodes collect and digitize the fluorescence to produce an emission spectrum.

CALIBRATION

A background spectrum, to be subtracted from the acquired patient data at the corresponding excitation wavelengths, was obtained at all 3 excitation wavelengths consecutively with the probe immersed in a nonfluorescent bottle filled with distilled water. Then, 1 fluorescence spectrum was measured at each excitation wavelength with the probe placed on the surface of a quartz cuvette containing a solution of rhodamine 610 dissolved in ethylene glycol (2 mg/L).

The detection system produces a nonuniform spectral response because the collection efficiency of the system is wavelength dependent. To correct for this, the spectrum of a known standard was recorded, and correction factors were derived from this spectrum. These factors were obtained by recording the spectrum of a National Institute of Standards and Technology traceable calibrated tungsten ribbon filament lamp. Corrected spectra from each site at each excitation wavelength were averaged and divided by the peak fluorescence intensity of the rhodamine 610 calibration standard at the corresponding excitation wavelength. Thus, the data illustrated in this article are not the absolute fluorescence intensities of the tissues but rather the intensities relative to the rhodamine 610 standard.

DATA ACQUISITION

The probe was disinfected with Metricide (Metrex Research Corp, Parker, Colo) before use in accordance with standard protocol. The probe was then guided into the oral cavity, and its tip was positioned flush with the mucosa. The probe projected the laser light onto the tissue surface at the 337-, 365-, and 410-nm excitation wavelengths sequentially. The tissue fluorescence was delivered through the collection fibers to the detection system where emission spectra were collected.

Five spectra for 5 consecutive pulses were measured at each excitation wavelength. Fluorescence spectra were obtained from each site at a resolution of 10 nm (full width at maximum) and a signal-to-noise ratio of approximately 30:1 at the fluorescence maximum at each excitation wavelength.

Fluorescence spectra were obtained from 8 healthy volunteers at 9 sites within the oral cavity (Table 1). In 6 of 8 volunteers, spectra were obtained bilaterally. No biopsy samples were obtained from volunteers.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Table 1. Comparison of Peak Intensities Among Different Oral Cavity Sites*

	Wavelength, nm		
Site	410	365	337
HP	0.71	0.77	1.70
SP	0.60	1.05	2.01
VT	0.55	0.58	1.71
RMT	0.51	0.86	1.79
FOM	0.47	0.76	1.65
BM	0.47	0.76	1.47
DT	0.26	0.36	1.07
LT	0.24	0.70	1.17
G	0.23	0.51	1.60

**The mean peak intensity for each site at each wavelength is shown. Wavelength 410: the 3 sites with highest mean peak intensities (HP, SP, and VT) were significantly greater than the 3 lowest (DT, LT, and G) at the .05 level of significance (or less). Also, the RMT mean was significantly greater than that of G. Wavelength 365: only the highest mean (SP) was significantly greater than the lower mean (DT). Wavelength 337: the mean peak intensity for SP was significantly greater than LT and DT, and the mean for RMT was significantly greater than DT. No other significant differences between mean peak intensities by sites were found. HP indicates hard palate; SP, soft palate; VT, ventral tongue; RMT, retromolar trigone; FOM, floor of mouth; BM, buccal mucosa; DT, dorsal tongue; LT, lateral tongue; and G, gingiva.*

Table 1. Comparison of Peak Intensities Among Different Oral Cavity Sites*

In the 15 patients, a clinical diagnosis of each lesion as normal, abnormal (not dysplastic or dysplastic), or cancerous was recorded by an experienced head and neck surgeon (A.G.) or a dental oncologist (R.J.). Spectra were measured from clinically normal and abnormal oral sites in the clinic or in the operating room before surgical resection of oral lesions (Table 2). Spectra were obtained from sites within a lesion and from a contralateral, clinically normal site. After spectroscopy, a 2- to 4-mm biopsy specimen of the tissue was taken from where the probe measured the spectra. These specimens were evaluated by an experienced pathologist (B.K.) using light microscopy and were classified as normal, mucosal reactive atypia, dysplasia, or cancerous using a standard diagnostic criterion. Biopsy samples with multiple diagnoses were classified according to the most severe pathologic diagnosis. The pathologists and clinicians were unaware of the results of the spectroscopic analyses.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Table 2. Patient Information Summary*

Patient No.	Site	Pathologic Diagnosis	Inflammation	Clinical Impression	Intensity at 337 nm	Red-Blue Ratio at 410 nm
1	Lateral tongue	CA	Mod	CA	Ab	Nml
		Nml	None	Nml	Nml	Nml
2	Ventral tongue	MRA	Mild	Ab-ND	Ab	Ab
		Nml	None	Nml	Nml	Nml
3	Lateral tongue	Dys	Min	CA	Nml	Ab
		Nml	None	Nml	Nml	Nml
4	Ventral tongue	CIS	NA	CA	Ab	Ab
		Nml	None	Nml	Nml	Nml
5	Ventral tongue	CA	Mod	CA	Ab	Ab
		CA	Mod	Ab-Dy	Ab	Nml
		Nml	Min	Nml	Nml	Nml
6	Buccal mucosa	Dys	Mod	CA	Ab	Ab
		Dys	Mod	Ab-ND	Ab	Nml
		Dys	None	Ab-ND	Ab	Ab
		Nml	None	Nml	Nml	Nml
7	Hard palate	Dys	NA	CA	Ab	Ab
		Nml	None	Nml	Nml	Nml
8	Ventral tongue	CIS	Sev	CA	Ab	Ab
		Dys	Mod	CA	Ab	Ab
		Nml	None	Nml	Nml	Nml
9	Gingiva	CA	Mild	CA	Ab	Ab
		Nml	Mild	Nml	Nml	Nml
	Buccal mucosa	CA	None	CA	Ab	Ab
		Nml	Yes	Nml	Nml	Nml
10	Lateral tongue	CA	Mild	CA	Ab	Ab
		CIS	Mod	CA	Ab	Ab
		Dys	Mild	Ab-ND	Nml	Ab
		Nml	Sev	Nml	Nml	Nml
11	Lateral tongue	CA	Mod	CA	NA	NA
		Dys	Mod	Nml	NA	NA
12	Floor of mouth	CA	Mod	CA	NA	NA
		CA	Mild	CA	NA	NA
		MRA	Mild	Nml	NA	NA
13	Ventral tongue	Dys	Mild	Nml	NA	NA
		MRA	Mod	CA	NA	NA
		MRA	Mild	CA	NA	NA
		MRA	Mild	CA	NA	NA
		Nml	Mod	Nml	NA	NA
14	Ventral tongue	Nml	None	Dys	NA	NA
		Dys	Yes	Dys	NA	NA
		Dys	Sev	Dys	NA	NA
		Nml	None	Nml	NA	NA
15	Retromolar trigone	CA	Mod	CA	NA	NA
		Dys	None	Nml	NA	NA
	Gingiva	Dys	Mod	Dys	NA	NA
		Nml	None	Nml	NA	NA

*CA indicates cancer; Nml, normal; MRA, mucosal reactive atypia; Dys, dysplasia; CIS, carcinoma in situ; Mod, moderate; Min, minimal; NA, not assessed; Sev, severe; Ab-ND, abnormal (not dysplastic); Ab-Dy, abnormal (dysplastic); and Ab, abnormal.

Table 2. Patient Information Summary*

DATA ANALYSIS

Spectral data from the healthy volunteers were analyzed to determine the amount of variance in the fluorescence intensities and line shape of normal tissue (1) within a particular location in each subject, (2) among different anatomical locations in each subject, and (3) among subjects by site. Specifically, an analysis of the peak fluorescence intensities at the various sites and of the ratios of the intensities at the red (635-nm) and blue (455-490–nm) regions of the spectrum was made. An analysis of variance was performed to determine whether the average peak fluorescence intensity for all healthy volunteers differed among sites at each excitation wavelength.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Spectral data from patients were analyzed to detect variance in the fluorescence intensities and spectral line shape. For each patient, peak fluorescence intensities from abnormal sites were compared with those from normal sites. A similar comparison was made using a ratio of the fluorescence intensities at the red and blue regions. The intensity in the red region was measured at 635-nm emission for all excitation wavelengths because most red peaks occur at this wavelength. The intensity in the blue region was measured at 455 nm for 337- and 365-nm excitation wavelengths because most spectra produced a blue peak at 455 nm. At the 410-nm excitation wavelength, however, most of the peaks occurred at 490 nm; thus, the blue region data were measured at 490 nm for this excitation wavelength.

Abnormal samples were those histologically classified as mucosal reactive atypia, dysplasia, or cancer. Normal samples were those histologically classified as normal.

RESULTS

HEALTHY VOLUNTEERS

Fluorescence spectra were acquired from 95 sites in 8 healthy, nonsmoking volunteers.

Contralateral Sites—Same Subject

The peak fluorescence intensity at 337-nm excitation of contralateral sites on the lateral tongue in healthy volunteers is shown in Figure 1, A. Data from 2 volunteers are not shown in these figures because their spectra were only obtained unilaterally. In Figure 1, B, the peak intensity at each site has been normalized by the peak intensity of the right side in each patient (the left-side intensity was divided by the right-side intensity, making all right-sided intensities equal to 1). The average normalized peak intensity of the left side was 1.06, with an SD of 0.21. We, therefore, chose 1.21 (1 plus 1 SD) as the cutoff value for normal with the peak fluorescence intensity at the 337-nm wavelength. Using the cutoff value, 4 of 6 normal sites were classified as normal.

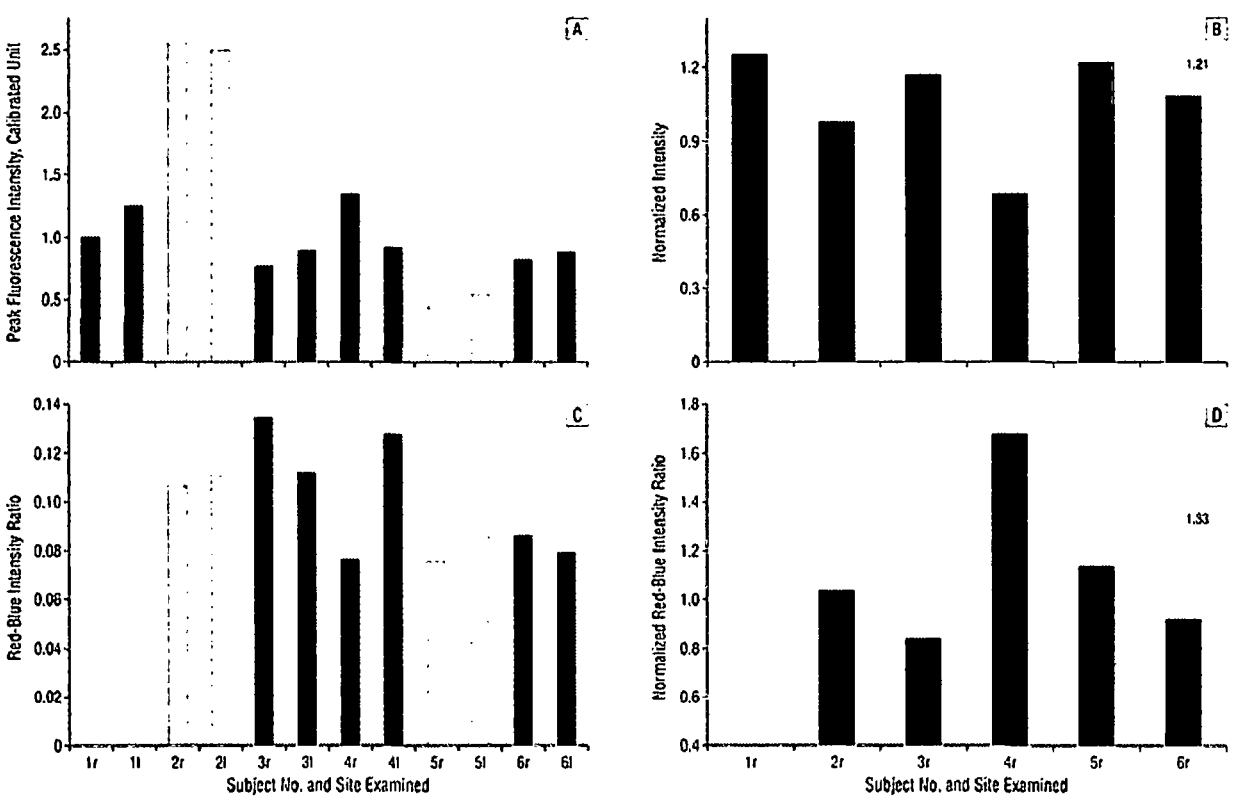


Figure 1. A, Peak fluorescence intensities at the 337-nm excitation wavelength of bilateral tongue

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

sites in 6 healthy volunteers. B, Peak intensities in (A) have been normalized to the right site value in each patient. The average normalized peak intensity of the left side was 1.06 within an SD of 0.121. A cutoff value of 1.21 (1 plus 1 SD) was chosen for normal for peak intensities at 337 nm. C, Peak fluorescence intensities in bilateral soft palate sites in 5 healthy volunteers at the 410-nm excitation wavelength. The data from patient 1 at this wavelength were unavailable because of investigator error. D, Data in (C) have been normalized to the right site value in each patient. A cutoff value of 1.22 (1 plus 1 SD) was chosen for normal for the 410-nm wavelength. r indicates right; l, left.

The ratio of intensities at the red and blue spectral regions for spectra at each excitation wavelength were also compared; Figure 1, C and D, illustrate results at the 410-nm excitation. Figure 1, C, illustrates the red-blue intensity ratio of contralateral sites on the soft palate at the 410-nm excitation. In Figure 1, D, the red-blue intensity ratio has been normalized (the red-blue intensity ratio on the left side was divided by the right-side red-blue intensity ratio, making all right-sided ratios equal to 1). The average normalized red-blue intensity ratio of the left side was 1.12, with an SD of 0.33. We, therefore, chose 1.33 (1 plus 1 SD) as the cutoff value for normal using the red-blue intensity ratio at the 410-nm wavelength. Using this cutoff value, 4 of 5 normal sites were classified as normal. The red-blue intensity ratios in general showed less variation between sites or between patients than did the peak intensities; the least variation was observed at the 410-nm excitation wavelength.

Multiple Oral Sites

An analysis of variance was made separately for each wavelength (337, 365, and 410 nm) to determine whether the average peak fluorescence intensity differed among sites at each excitation wavelength. The independent variable of sites was significant for 2 of 3 wavelengths: $P = .05$ for 337 nm (barely significant), $P = .23$ for 365 nm (not significant), and $P<.001$ for 410 nm (significant). However, most sites did not differ from each other. The Duncan multiple range test was used to determine which pairs of sites tend to differ. This method takes into account the number of tests made and controls the overall type I error rate to no more than 5%. These results are illustrated in Table 1. In general, the person-to-person variation at each site was greater than the contralateral variation within a particular site in the same person and the variation among different anatomical sites within the same person.

PATIENTS

Spectroscopic data were obtained from 45 sites in 15 patients. Data from 3 patients were excluded because of instrumentation error: the spectral readings were uninterpretable secondary to oversaturation of the diode array. In the remaining 12 patients, 33 sites were examined clinically, spectroscopically, and histologically (Table 2). In 2 patients, the clinically normal sites were abnormal on histological evaluation, preventing a comparison between normal and abnormal sites within these 2 patients.

Typical spectra from normal and abnormal areas are shown in Figure 2, A. The greatest intensity occurred in the blue region between 455 and 490 nm (blue peak). The blue peak from normal tissue is visibly greater than that from abnormal tissue. When the spectra of both areas were normalized (the line curves were adjusted so that the peak intensity of the abnormal and normal samples have the value of 1), changes in spectral line shape became evident (Figure 2, B). The line-shape differences were predominantly because of increased fluorescence of abnormal tissues in the red region (red peak at 635 nm) and a shift of the peak intensity of abnormal tissues to a longer wavelength. Spectra from all 3 wavelengths demonstrated consistent differences in peak intensity and spectral line shape between normal and abnormal tissue. The 365-nm excitation wavelength produced the least discrimination. Because the greatest spectral variance occurred in the blue (455-490 nm) and red (635 nm) regions, these 2 areas were chosen for further analysis.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

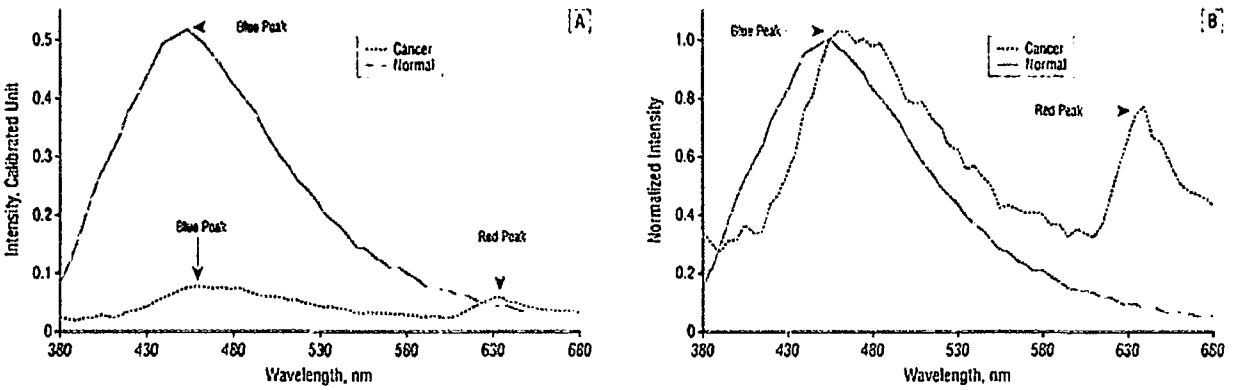


Figure 2. A, Spectra obtained from normal and cancerous sites in 1 patient at the 365-nm excitation wavelength. B, Same data as in (A) except that the intensity of the cancer spectrum is now normalized to that of the spectrum from the normal sample. Note the shift of the peak intensity to a longer wavelength and the increased fluorescence of the abnormal tissue in the red region. Similar findings were obtained at 337- and 410-nm excitation wavelengths.

To quantify the alterations in the spectra and to determine whether they were present in all patients, the intensities of the blue peaks of normal and abnormal sites were tabulated. For optimal data analysis, spectra should be obtained from contralateral normal and abnormal sites in each patient. This occurred in 10 of 12 evaluable patients. The remaining 2 patients had clinically normal samples that were deemed dysplastic or mucosal reactive atypia on histological evaluation. The data from these 2 patients appear last in Figure 3 and Figure 4 and were not used in analyzing the sensitivity and specificity of the diagnostic algorithms.

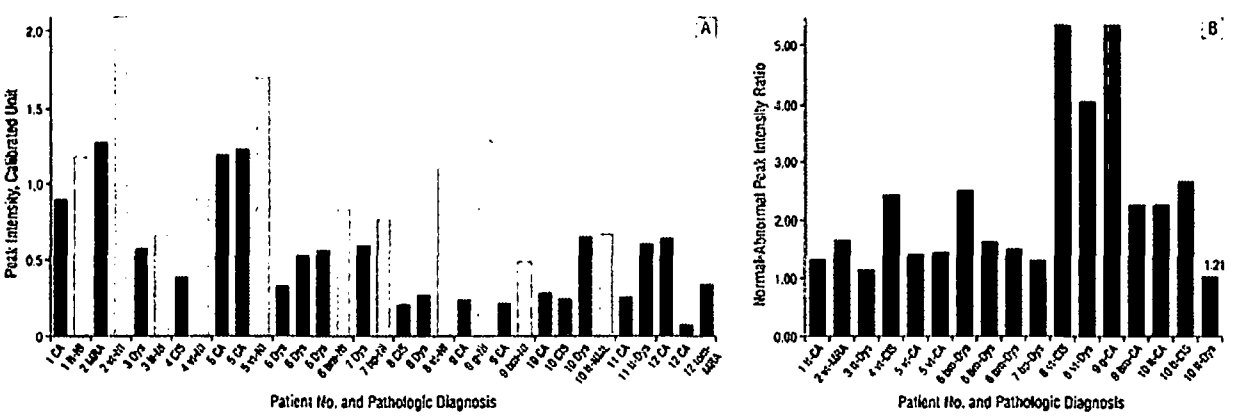


Figure 3. A, Comparison of peak intensities of histologically abnormal samples (black bars) and histologically normal samples (white bars) at the 337-nm excitation wavelength. Although there is interpatient variability, the intensities of the abnormal samples are less than those of their normal control sample. B, A normal-abnormal peak intensity ratio is obtained by dividing each normal sample's peak intensity by the corresponding abnormal sample's peak intensity. In 15 of 17 sites, this ratio is greater than 1.21 (the calculated normal cutoff value from Figure 1, B). CA indicates cancer; lt, lateral tongue; Nl, normal; MRA, mucosal reactive atypia; vt, ventral tongue; Dys, dysplasia; CIS, carcinoma in situ; bm, buccal mucosa; hp, hard palate; g, gingiva; and fom, floor of mouth.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

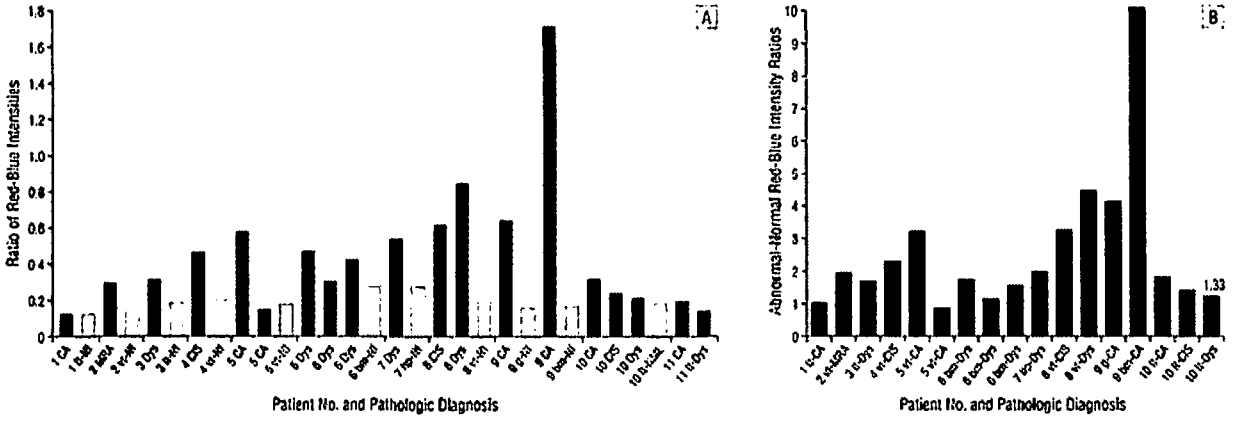


Figure 4. A, Comparison of the ratio of intensities at the red (635-nm) and blue (490-nm) regions at the 410-nm excitation wavelength. Despite patient-to-patient variability, it is evident that this ratio in abnormal tissue (black bars) is greater than the ratio in the corresponding normal tissue (white bars). The data from patient 12 are missing for this wavelength because of investigator error. B, Ratio of abnormal red-blue intensity divided by normal red-blue intensity. This ratio was greater than 1.33 (the calculated normal cutoff value from Figure 1, D) in 13 of 17 sites. Abbreviations are explained in the legend to Figure 3.

Figure 3, A, shows the peak intensities of abnormal and normal samples at the 337-nm excitation wavelength. In 9 of 10 patient sites, the peak fluorescence intensities of normal sites were greater than those of all histologically abnormal sites; in the 10th patient, the peak intensity of the normal site was greater than that of 2 of 3 abnormal sites. Because of considerable patient-to-patient variation in intensity, the separation between normal and abnormal intensity peaks could be better visualized when the ratios of the peak intensities of normal areas to abnormal areas were calculated for each abnormal site (Figure 3, B). In 15 of 17 sites, this ratio was 1.21 or greater (1 plus 1 SD, as shown in Figure 1, B). The magnitude of the difference between normal and abnormal (the size of the ratio) did not seem to vary with increased severity of disease. Although results are shown only for the 337-nm excitation scans, similar results were obtained at all excitation wavelengths.

The ratios of the peak intensities in the red vs blue region (red-blue peak ratios) were also used to compare normal with abnormal tissues. The red-blue peak ratios were greater in abnormal tissues than in contralateral normal sites within the same patient (Figure 4, A). Again, patient-to-patient variation was high. As shown in Figure 4, B, the ratio of abnormal to normal red-blue peak ratios was greater than 1.00 in 16 of 17 sites. This ratio was greater than 1.33 (1 plus 1 SD) in 13 of 17 sites. Although results are shown only for the 410-nm excitation scans, similar results were obtained at all excitation wavelengths.

In Figure 5, the same data shown in Figure 3, B (x-axis), and Figure 4, B (y-axis), are presented in a scattergram to illustrate the effect of combining these 2 algorithms based on the peak intensities at 337 nm and the red-blue peak ratios at 410 nm. Whereas each algorithm alone misclassified several abnormal sites as normal (ie, the abnormal site fell below the chosen normal cutoff value), when the 2 algorithms are combined, only 1 abnormal site was misclassified as normal by both algorithms.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

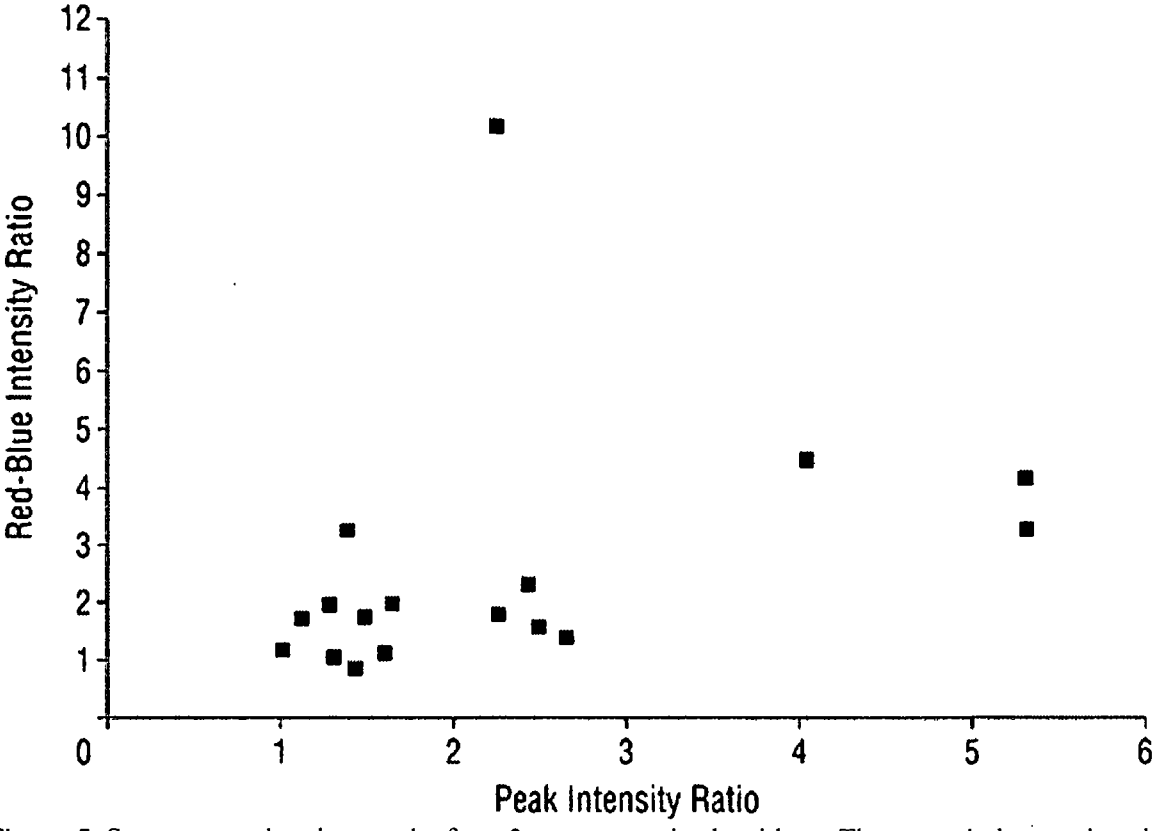


Figure 5. Scattergram showing results from 2 spectroscopic algorithms. The normal-abnormal peak intensity ratio at 337 nm (Figure 3, B) is plotted on the x-axis and the normal-abnormal red-blue intensity ratio at 410 nm (Figure 4, B) is plotted on the y-axis. Note that 1 site falls completely below both normal cutoff values.

Our data from healthy volunteers and patients suggest that fluorescence spectroscopy can be used to identify pathologic abnormalities in the oral mucosa. Using data from the first 10 patients in whom pathologic and spectroscopic data from an abnormal site and a corresponding normal site were available, we developed 2 simple diagnostic algorithms based on peak fluorescence intensity at the 337-nm excitation and the red-blue intensity ratio of the 410-nm excitation. A third diagnostic algorithm was made by combining the first 2 algorithms. A comparison of the sensitivity and specificity of these diagnostic algorithms is given in Table 3. The pathologic diagnosis was used as the criterion standard.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Table 3. Sensitivity and Specificity of 3 Spectroscopic Diagnostic Algorithms

	Sensitivity, %	Specificity, %
Clinical impression	76.5	100.0
Normalized peak intensity at 337 nm	88.2	100.0
Normalized red-blue peak ratio at 410 nm	76.5	100.0
Combined normalized peak intensity at 337 nm and red-blue peak ratio at 410 nm	94.1	100.0

	Pathologic Diagnosis	
	Abnormal	Normal
Clinical impression		
Abnormal	13	0
Normal	4	11
Spect 337		
Abnormal	15	0
Normal	2	11
Spect 410		
Abnormal	13	0
Normal	4	11
Spect 337 + 410		
Abnormal	16	0
Normal	1	11

Table 3. Sensitivity and Specificity of 3 Spectroscopic Diagnostic Algorithms

If the clinical diagnosis was normal or abnormal (not dysplastic) and the pathologic diagnosis was normal, then the clinical impression was characterized as a true-negative. Otherwise it was classified as a false-negative. If the clinical diagnosis was abnormal (dysplastic) or cancerous and the pathologic diagnosis was normal, then the clinical impression was classified as a false-positive. Otherwise it was classified as a true-positive. Using these criteria, visual examination by an experienced practitioner (A.G. and R.J.) detected oral neoplasia or dysplasia with a sensitivity and specificity of 76.5% and 100.0%, respectively. All study patients had been referred to a cancer center because of a pathologic diagnosis or suspicion of cancer, and this most likely affected the clinician's index of suspicion for malignant lesions.

Figure 1, B, shows that the normalized peak intensity of 4 of 6 normal sites at the 337-nm excitation is less than 1 plus 1 SD (1.21). Using this value as a cutoff point to classify unknown sites as normal or abnormal yielded a sensitivity of 88.2% and a specificity of 100.0%. Similarly, Figure 1, D, shows that the normalized red-blue peak ratio at 410 nm of all but 1 site is less than 1 plus 1 SD (1.33). Using this value as a cutoff point to classify unknown sites as normal or abnormal gave a sensitivity of 76.5% and a specificity of 100.0%. Combining these 2 criteria, and identifying those samples as abnormal that exceed at least 1 criterion, yielded a sensitivity of 94.1%, an increase compared with the sensitivity of each algorithm alone.

COMMENT

The results of this study demonstrate the ability of fluorescence spectroscopy to differentiate between neoplastic and nonneoplastic oral cavity tissue in vivo. Comparisons of neoplastic and nonneoplastic sites within patients revealed differences in spectral intensities and line shapes at 3 excitation wavelengths (337, 365, and 410 nm) that may be exploited to noninvasively identify neoplastic oral lesions. In general, the peak fluorescence intensities of abnormal sites were less than those of normal sites. The fluorescence intensities of abnormal sites were increased in the red spectral region

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

compared with those of normal sites. Although differences were noted at all 3 wavelengths, the 337- and 410-nm wavelengths provided the best discrimination between normal and abnormal in this study.

The specific alterations in tissue architecture or biochemical composition causing the overall decrease in fluorescence intensity of neoplastic and dysplastic tissue have not been elucidated. Natural fluorophores that may undergo changes in quantity or form during neoplastic progression include flavins, nicotinamide adenine dinucleotide (NADH), and collagen.9 Some decreased fluorescence intensity of abnormal specimens, as illustrated in Figure 2, may be attributed to an increase in hemoglobin absorption.

Our results confirm and expand the findings of previous investigations. Dhingra et al10 analyzed spectra from oral cavity lesions obtained in vivo at the 370- and 410-nm excitation wavelengths. As in the present study, this group also found decreased peak intensities in pathologically abnormal vs normal tissues and increased intensity in the red region of abnormal vs normal tissues. An assessment of the sensitivity and specificity of diagnostic algorithms using these wavelengths was not presented, however. An earlier clinical trial by Savage et al11 measured 2 fluorescence emission spectra at the 300- and 340-nm excitation and 2 excitation spectra at 380- and 450-nm emission from healthy volunteers and patients with lateral tongue cancer. This group used intensity ratios at various wavelengths (including the red-blue ratio) to discriminate between malignant and normal tongue tissue; no dysplastic lesions were examined.

In addition, results of an in vitro study of oral mucosa by Roy et al12 also showed consistent spectral differences when dysplastic and cancerous tissue were compared with normal tissue. This group found that spectral differences were most prominent at the 410-nm excitation wavelength. All abnormal spectra exhibited increased fluorescence in the red region (>600 nm). Similar results were presented by Ingrams et al.13

In our investigation, the 410-nm excitation wavelength produced the greatest number of red shifts (peaks of abnormal samples in the 635-nm region), which, when used in conjunction with the lower peak intensities in the blue region of the neoplastic tissue, provide an excellent signature for abnormal samples. Because only 3 wavelengths were evaluated, the possibility remains that other wavelengths not yet tested would provide greater discrimination between normal, inflammatory, and neoplastic tissue. Unlike in other studies (Roy et al12), a visible red shift did not occur for all our subjects, but it was noted more frequently at the 410-nm excitation wavelength. The exact cause of the red shift is not known, although currently it is attributed to porphyrins.14,15 The fluorescence maximum of porphyrin is closest to the 410-nm excited spectra obtained in this study. It remains unclear whether the red shift is caused by increased porphyrin content within cancerous cells or some other cause, such as increased porphyrin secondary to bacterial synthesis within necrotic tissue. Several bacteria, such as *Escherichia coli*, *Klebsiella pneumonia*, and *Staphylococcus pyogenes*, among others, are known to produce porphyrin and to induce red fluorescence.14

The results of this study are important because they demonstrate the diagnostic potential of fluorescence spectroscopy for the diagnosis of early neoplastic lesions of the oral mucosa. The development of an optical spectroscopy system that can differentiate normal, inflammatory, and neoplastic samples based on autofluoresence alone would be a tremendous clinical advance. By avoiding the need for introduction of exogenous dyes, invasive procedures, and clinical diagnostic experience, this technology could make possible low-cost mass screening for oral neoplasia in settings such as primary care and dental clinics. In addition, in patients with previous malignant lesions of the aerodigestive tract, such a system could greatly augment the ability to adequately follow up patients for the development of second primary lesions.

However, the data presented in this report were obtained from a small number of volunteers and patients. The algorithms developed so far seem promising for discriminating between normal and abnormal tissue, but they cannot distinguish between mucosal reactive atypia, dysplasia, and frank

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

carcinoma. In addition, the algorithms require a comparison of abnormal tissue to a corresponding normal site within the same patient. Any method developed for analysis should take into account that the patient-to-patient variation of healthy volunteers is great and that the variation within a particular location in each person is small. Thus, any comparison of normal to abnormal tissues should focus within a single patient. The need exists for further study with more patients and volunteers to develop diagnostic algorithms that can adequately differentiate between normal, inflammatory, premalignant, and malignant oral mucosal tissue.

AUTHOR INFORMATION

Accepted for publication September 15, 1997.

Presented at the 4th International Conference on Head and Neck Cancer, Toronto, Ontario, August 1, 1996.

We thank Glenn Criswell and the patients and staff of the Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, for assistance with data acquisition and Jude Richard for editorial assistance.

Reprints: Ann Gillenwater, MD, Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 69, Houston, TX 77030.

From the Departments of Head and Neck Surgery (Drs Gillenwater, Jacob, and Clayman), Pathology (Drs Kemp and El-Naggar), Biomathematics (Dr Palmer), and Gynecologic Oncology (Dr Follen Mitchell), The University of Texas M. D. Anderson Cancer Center, Houston; and the Biomedical Engineering Program, The University of Texas, Austin (Drs Ganeshappa and Richards-Kortum).

REFERENCES

1. Silverman S, Migliorati C, Barbosa J. Toluidine blue staining in the detection of oral precancerous and malignant lesions. *Oral Surg Oral Med Oral Pathol.* 1984;57:379-382. FULL TEXT | ISI | PUBMED

2. Rosenberg D, Cretin S. Use of meta-analysis to evaluate tolonium chloride in oral cancer screening. *Oral Surg Oral Med Oral Pathol.* 1987;67:621-627.

3. Epstein J, Scully C, Spinelli J. Toluidine blue and Lugol's iodine application in the assessment of oral malignant disease and lesions at risk of malignancy. *J Oral Pathol Med.* 1992;21:160-163. FULL TEXT | ISI | PUBMED

4. Romer TJ, Fitzmaurice M, Cothren RM, et al. Laser-induced fluorescence microscopy of normal colon and dysplasia in colonic adenomas: implications for spectroscopic diagnosis. *Am J Gastroenterol.* 1995;90:81-87. ISI | PUBMED

5. Ramanujam N, Mitchell MF, Mahadevan A, et al. In vivo diagnosis of cervical intraepithelial neoplasia using 337 nm excited laser-induced fluorescence. *Proc Natl Acad Sci U S A.* 1994;91:10193-10197. **FREE** FULL TEXT

6. Ramanujam N, Mitchell MF, Mahadevan A, et al. Development of a multivariate statistical algorithm to analyze human cervical tissue fluorescence spectra acquired in vivo. *Lasers Surg Med.* 1996;19:46-62. FULL TEXT | ISI | PUBMED

7. Hung J, Lam S, LeRiche JC, Palcic B. Autofluorescence of normal and malignant bronchial tissue. *Lasers Surg Med.* 1991;11:99-105. ISI | PUBMED

8. Alfano RR, Pradhan A, Tang GC. Optical spectroscopic diagnosis of cancer and normal breast tissues. *J Opt Soc Am A.* 1989;6:1015-1023.

9. Richards-Kortum R, Sevick-Muraca E. Quantitative optical spectroscopy for tissue diagnosis. *Annu Rev Phys Chem.* 1996;47:555-606. FULL TEXT | ISI | PUBMED

10. Dhingra JK, Perrault DF Jr, McMillan K, et al. Early diagnosis of upper aerodigestive tract cancer by autofluorescence. *Arch Otolaryngol Head Neck Surg.* 1996;122:1181-1186. ABSTRACT

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

11. Savage H, Kolli V, Ansley J, Chandawarkar R, Alfano R, Schantz S. Innate tissue fluorescence of the oral mucosa of controls and head and neck cancer patients. In: Alfano RR, ed. *Proceedings of Advances in Laser and Light Spectroscopy to Diagnose Cancer and Other Diseases II.* Bellingham, Wash: SPIE; 1995;2387:2-14.
12. Roy K, Bottril I, Ingrams D, et al. Diagnostic fluorescence spectroscopy of oral mucosa. In: Anderson R, ed. *Proceedings in Lasers in Surgery: Advance Characterization, Therapeutics and Systems V.* Bellingham, Wash: SPIE; 1995;2395:135-142.
13. Ingrams DR, Dhingra JK, Roy K, et al. Autofluorescence characteristics of oral mucosa. *Head Neck.* 1997;19:27-32. FULL TEXT | ISI | PUBMED
14. Harris D, Werkhaven J. Endogenous porphyrin fluorescence in tumors. *Lasers Surg Med.* 1987;7:467-472. ISI | PUBMED
15. Konig K, Schneckenburger H, Hemmer J, Tromberg B, Steiner R. In vivo fluorescence detection and imaging of porphyrin-producing bacteria in the human skin and oral cavity for the diagnosis of acne vulgaris, caries, and squamous cell carcinoma. In: Alfano RR, ed. *Proceedings of Advances in Laser and Light Spectroscopy to Diagnose Cancer and Other Diseases.* Bellingham, Wash: SPIE; 1994;2135:129-138.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

THE ROLE OF HUMAN PAPILLOMAVIRUS IN ORAL CARCINOGENESIS

Patrick K. Ha* Joseph A. Califano
The Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Medical Institutions, 601 N. Caroline St., 6th Floor, Baltimore, MD 21287;
*** corresponding author,** phal@jhmi.edu

Abstract

Human papillomavirus (HPV) infection with high-risk types 16 and 18 has widely been reported as one of the prominent mechanisms behind the development of cervical squamous cell carcinoma. Links between HPV and oral cavity cancer have been suggested as well, based on epidemiologic and molecular means, though the association is less well-established. It is likely that HPV plays a role in oral cavity carcinogenesis, though only in a small subset of cases. The difficulty in providing true causal evidence of HPV's role in oral cancer lies in our lack of understanding of the significance of mechanisms by which HPV leads to oral carcinogenesis, as well as limitations in the molecular analysis of HPV. Further studies are necessary for the contribution of HPV in oral cavity malignancy to be better demonstrated.

Key words. Head and neck cancer, pre-malignant

(I) The HPV Genome and Its Contribution to Malignancy

Human papillomavirus (HPV) is a ~ 7.9-kb, non-enveloped, double-stranded, circular DNA virus that has been implicated in a variety of anogenital and aerodigestive diseases, ranging from common warts to laryngeal papilloma to cervical cancer. The first isolation of these virus particles was performed in 1933 in rabbit papillomatosis (Shope, 1933). The extract from these lesions was found to contain infectious particles, and many of the benign papillomas in rabbits were observed to progress to malignancy. Currently, sequences for over 81 different types of HPV have been identified, with several additional poorly characterized types described. These viruses infect cells in the basal layer of squamous epithelium, and the different types have been traditionally separated based on tropism for cutaneous and mucosal sites, as well as high, intermediate, and low risk, depending on their association with malignancy (zur Hausen, 1996). For the purpose of this review, we will focus on mucosal high-risk types, known to be significant in the head and neck, predominantly HPV 16 and HPV 18. Many other types have been implicated in head and neck cancer, including 31, 33, 39, 45, 52, 58, and 69 (zur Hausen, 2000), though these have not been found to be highly significant in the majority of studies. Furthermore, many of the consensus polymerase chain-reaction (PCR) primers developed to detect the presence of HPV DNA will encompass many of the aforementioned types.

The HPV genome typically consists of nine open-reading frame sequences, located on only one of the strands of DNA, and is divided into seven early-phase genes (E) and two late-phase genes (L). The early genes serve to regulate the transcription of DNA, while the late genes encode for proteins involved in viral spread, such as capsid proteins (Stoler *et al.*, 1989). The E1 and E2 gene products are more specifically involved in regulating the transcription and replication of viral proteins. These different gene regions and gene products provide the basis on which molecular detection methods have been created.

The mechanism of HPV carcinogenesis was first identified in cervical cancer. Worldwide, greater than 90% of cervical cancers are related to HPV infection, with types 16 and 18 being implicated in the majority of cases (Walboomers *et al.*, 1999). HPV DNA sequences found in cervical carcinoma cell lines were the first clue to the role that high-risk types 16 and 18 play in altered cell growth

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(Schwarz *et al.*, 1985; Schneider-Gadicke and Schwarz, 1986; von Knebel Doeberitz *et al.*, 1988). Further studies in cervical cancer cell lines have demonstrated many of the harmful effects of HPV in terms of cellular mutations (Havre *et al.*, 1995; Liu *et al.*, 1997) and genomic integrity (Hashida and Yasumoto, 1991; White *et al.*, 1994).

The E6 and E7 oncoproteins are normally under control of E2 and E1 inhibitory genes. These genes can be deleted or altered upon integration, leading to unchecked transcription of E6 and E7 (Baker *et al.*, 1987). These proteins are then able to disrupt the function of *Rb* and *p53*, known tumor suppressor genes (Werness *et al.*, 1990). *p53* has been implicated in a wide variety of cancers (Hollstein *et al.*, 1991) and is known to be the target of many different viral particles (Levine, 1990). *p53* and *Rb* are tumor suppressor genes in that they regulate cell-cycle checkpoints at the G1 phase. If inactivated, cells are more prone to push through division and replication, even in the setting of harmful gene mutations, which can lead to malignancy.

The E6 gene is able to inactivate *p53* (Scheffner *et al.*, 1990) through association with E6 associated protein. This complex then interacts with *p53* and undergoes ubiquitin-dependent degradation of *p53* (Scheffner *et al.*, 1993). E7 is able to bind and interact with the *Rb* gene product (Dyson *et al.*, 1989). E7 has the ability to phosphorylate the *Rb* proteins, leading to degradation by ubiquitination (Boyer *et al.*, 1996). This subsequently leads to E2F activation, which produces a family of transcription factors leading to cell proliferation. Many other possible mechanisms have been discovered by which these proteins can induce malignancy such that their role in carcinogenesis is ensured (zur Hausen, 2000). It has been shown that *p53* sequence alterations are decreased in the setting of HPV infection, since there is an alterative means of *p53* silencing with the production of E6 (Werness *et al.*, 1990; Kessis *et al.*, 1993a,b; Gillison *et al.*, 2000). Many of these pathways have also been implicated in head and neck cancer as well, which supports the possibility that HPV may play a significant role in head and neck cancer, and specifically in oral cancer, though other mechanisms are clearly involved.

The majority of studies involving oral lesions do not separate out specific subsites within the oral cavity, though the most common sites are the following: lip, anterior third of the tongue, floor of mouth, hard palate, gingiva, and buccal mucosa. This is an important, but often confused, distinction from the oropharynx, which includes the soft palate, base of tongue, tonsillar region, and posterior pharynx. Since there is general agreement that oropharyngeal carcinomas, most specifically tonsillar cancers, are frequently associated with HPV (Gillison *et al.*, 2000), we will focus our discussion on oral squamous cell carcinomas.

The link between oral squamous cell cancer and HPV seems logical, given the viral propensity for epithelial cell involvement. This connection was first proposed when cytopathic effects of HPV (koilocytosis) were noted on light microscopy (Syrjanen *et al.*, 1983) of oral lesions. *In situ* hybridization later confirmed the presence of HPV DNA in oral pre-malignancies (4/5 leukoplakias) and malignancies (3/6 carcinomas), thereby suggesting a causal association of HPV and carcinogenesis in oral lesions as well (Loning *et al.*, 1985), though we will further elaborate on the controversy behind these early findings. There have also been reports of altered cytologic features consistent with HPV infection, including a lack of keratin (Wilczynski *et al.*, 1998).

Researchers also discovered that human keratinocytes expressing E6 and E7 genes from HPV 16 become immortal (Munger *et al.*, 1989), as do oral epithelial cells (Park *et al.*, 1991; Oda *et al.*, 1996; Munoz, 2000). Analysis of these cell-line data supports the possibility that HPV infection was not specific to anogenital epithelium and could affect oral epithelium as well.

The majority of studies of head and neck lesions have focused on HPV 16 and 18, since these are known to be high-risk in cervical cancer. Other types—such as 6, 11, and 33—have not been identified in many oral malignancies (Mork *et al.*, 2001), though they are significant in other types of head and neck lesions, such as laryngeal papillomas. HPV 16 and, to a lesser extent, HPV 18 are the

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

most widely implicated types in the oral literature and are therefore the focus of this review.

(II) Molecular Detection of HPV

While epidemiologic studies can draw an association between HPV seropositivity and oral cancer, it must also be demonstrated that HPV is present and functioning in these infected cells. There are many methods by which HPV can be detected, but every method has its strengths and weaknesses. Underlying all of the sensitive molecular assays is the problem of contamination. Miniscule amounts of RNA or DNA can theoretically be carried over from sample to sample by direct transmission on gloves or instruments, or could even be 'aerosolized'. Thus, even with compulsive isolation techniques, some contamination cannot always be ruled out.

Several studies have demonstrated the detection of antibodies to E6 and E7 in cervical cancer patients (Jochmus-Kudielka *et al.*, 1989), indicating an immune response to the virus. The frequency of seropositive individuals was higher in patients with HPV-associated genital lesions, but 18.1% of the control population had antibodies to E4, and 3.9% to E7 proteins. In a Colombian study, investigators found that 82% of patients with invasive cervical cancer had antibodies to HPV, while 56% of controls demonstrated seropositivity (Combita *et al.*, 2002). These findings suggest that there may be some biological role for HPV, given the formation of antibodies to these oncoproteins. However, in a small study of HNSC patients, only 11/92 (12%) had HPV antibodies to E6 or E7, while 10/288 (3.5%) of normal individuals had HPV seropositivity. None of the patients with oral tumors demonstrated seropositivity (Zumbach *et al.*, 2000). A more recent study on HPV 16 capsid antibody status noted a 2.3-fold higher risk of oral cancer development, though the authors conceded that the timing of serologic conversion could not be clearly linked to the acquisition of the oral carcinoma (Schwartz *et al.*, 1998). In other words, the presence of oral cancer may have preceded the development of HPV seroconversion. Furthermore, it is not known if antibody development to any region of the HPV genome is significant, or if there are particular antibodies that herald a worse prognosis.

Serologic studies have also been undertaken to detect the presence of HPV infection in an individual's lifetime. ELISA tests for serum antibody presence to HPV have been developed which correlate well with the presence of HPV DNA in cervical samples (Kirnbauer *et al.*, 1994; Carter *et al.*, 1996). However, without samples being tested directly for the presence of HPV, it is impossible for the anatomic site infected to be pinpointed, and there remains a variable rate of endemic HPV seropositivity among 'normal' individuals. Furthermore, antibody presence is not necessarily indicative of active infection, latent integration, or oncoprotein production that might be a clinically significant contributor to carcinogenesis. In addition, seropositivity may be a confounding factor associated with other risk factors for oral cancer, including tobacco and ethanol exposure.

Assays for the E6 mRNA as well as HPV DNA have been performed. Such studies involving RNA are less common, since they require fresh-frozen tissue, which is not as readily available as archived paraffin tissue. Recently, by polymerase chain-reaction (PCR), one study demonstrated HPV DNA in 20/84 HNSC and E6 mRNA transcript in only 9/20 of these samples (van Houten *et al.*, 2001). This study highlights our lack of understanding of the HPV life cycle, and that presence of DNA may not necessarily indicate active viral production. It is also possible that HPV can be a transient infection, that may or may not participate in the foundation of malignancy. In cervical cancer patients, it has been discovered that HPV DNA presence often declines with time (Hildesheim *et al.*, 1994; Evander *et al.*, 1995), indicating that there may be early effects on cellular function initiated by HPV that would lead to carcinogenesis, but would not be detected by traditional molecular biology techniques. In other words, HPV may initiate a genetic 'hit' and then disappear. There has been a suggestion that HPV in the oral cavity does not necessarily integrate into the host genome and may reside in an episomal form (Maitland *et al.*, 1987; Watts *et al.*, 1991; Yeudall and Campo, 1991). However, it is

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

not clear that integration must occur for HPV to play a role in carcinogenesis. In cervical cancer, it is possible that HPV exists in a dormant state and does not necessarily need to produce mRNA continuously to maintain a malignant state (Lehn *et al.*, 1985).

In situ hybridization (ISH) involves the use of type-specific radioactively labeled DNA probes complementary to HPV sequences for detection. It was the initial assay of choice for HPV DNA before more sensitive molecular techniques were invented. While these studies piqued the interest of investigators, the validity of the prevalence data provided by these studies is unproven (McKaig *et al.*, 1998). The sensitivity of this assay was found to be at least on the order of 20-50 copies *per* cell (Syrjanen *et al.*, 1988a). However, ISH depends on the consistency of the complementary sequence present in the sample, and it is known that the presence of HPV DNA in oral cavity samples is inconsistent. Furthermore, storage of samples and degradation of signal over time are also issues, as is intra-observer variability.

PCR is known to be a very sensitive assay for the detection of HPV DNA in any given sample (Shibata *et al.*, 1988). Universal primers to conserved DNA sequences in HPV have been designed to the L1 region (also known as MY09/MY11) (Snijders *et al.*, 1991), the E1 region (also known as CPI and CPII) (Gregoire *et al.*, 1989; Tieben *et al.*, 1993), the E6 region (Maitland *et al.*, 1989), and the E7 region (Evander and Wadell, 1991). Furthermore, there is a host of other primers utilized that can be type-specific. The use of consensus primers *vs.* type-specific primers would theoretically result in a higher detection rate, since many different types of HPV would be identified. However, one study compared the use of type-specific E6 and E7 primers to L1 consensus primers, and there was no difference in detection rates (Resnick *et al.*, 1990), even though there is a theoretical advantage to using E6 and E7, since these are the known oncogenic proteins with specific molecular downstream effects related to carcinogenesis. This finding is perhaps due to the overwhelming prevalence of HPV-16 and, secondarily, HPV-18, to the exclusion of other types of HPV in the head and neck. A different study in cervical carcinoma samples noted that using several primer sets spanning the different regions would provide a more accurate determination of HPV prevalence (Karlsen *et al.*, 1996).

To add to the complexity, one study suggested that the use of consensus primers to the L1 and L2 regions would yield false-negative results, since these areas are disrupted upon viral integration into the host genome (Cruz *et al.*, 1996). Universal primers to the E1 or E2 region may also underestimate the true prevalence of HPV, since there is the possibility that these early-phase regions are disrupted upon integration (Resnick *et al.*, 1990). The majority of studies have settled on the use of MY09/11 primers for detection, which yields a product size of ~ 450 base pairs. In addition to the possibility of false-negatives due to primer selection, there is also a chance of sample contamination, even with the most careful of methods of tissue handling and processing (Paz *et al.*, 1997). In such a situation where contamination can be problematic, PCR does not offer as many possible means to control for this error, since it provides simply a binary finding. Those studies utilizing Southern blot or quantitative PCR techniques with fluorescent probes offer a means of quantification to differentiate low-level positivity from contamination.

Southern blot has long been one of the gold standard assays for the detection of HPV DNA. It offers the ability to distinguish between episomal and integrated DNA, and it can detect up to 0.1 copy *per* cell (Syrjanen, 1990). While it does have some technical variability (Brandsma *et al.*, 1989) and requires a significant amount of DNA, it is not as prone to contamination error. While Southern blot may boast a theoretically higher specificity, it is clearly less sensitive than PCR (Schiffman, 1992; Frazer *et al.*, 1993). One study utilizing both Southern blot and type-specific PCR for HPV 16/18 discovered that there was a marked difference in prevalence when these different methods were used (Yeudall and Campo, 1991). Two of 39 oral carcinoma samples were positive for either HPV 16/18 by Southern blot, whereas 18/39 were positive by type-specific PCR for HPV 16/18. The authors additionally sampled adjacent dysplasia and normal mucosa from these same patients, and by Southern blot, all samples were negative, whereas only 2 samples did not demonstrate HPV by PCR

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

in these adjacent samples. This study clearly demonstrates the difference in sensitivity of these two assays and raises the further question of what threshold of HPV infection is adequate for carcinogenesis. In addition, Gillison *et al.*(2000) utilized consensus PCR and Southern blot and discovered that, in non-oropharyngeal tumors, Southern blot was rarely positive when compared with PCR.

A recent study used the advantages of quantitative PCR and analyzed oral tumor samples previously found to be HPV-positive by other molecular means (Ha *et al.*, 2002) as well as pre-malignant oral cavity lesions. Quantitative PCR utilizes a fluorescent probe that is cleaved upon each round of amplification by the DNA polymerase, and the degree of fluorescence in the reaction mixture is then measured. The ability to quantify the amount of HPV present allows one to set a threshold for a significant infection. The theory of clonal expansion would suggest that at least one viral copy is needed *per* cell. In this study, it was discovered that samples found to be positive by Southern blot were also uniformly positive by quantitative PCR, but those found to be positive by traditional PCR alone were below the threshold of detection by quantitative PCR. Thus, this technique combines the sensitivity of PCR with additional specificity as a result of one's ability to quantify viral particles *per* cell.

As the field of HPV has developed, researchers have utilized techniques for detection that have taken advantage of the most recent technology both directly for DNA or for other surrogate markers of infection. However, no method is without flaws, and it remains unclear what the molecular significance of HPV DNA detection is with regard to carcinogenesis. Critical evaluation of data based on the types of detection methods used as well as determination of what the data mean in a clinical context is necessary for appropriate analysis.

(III) HPV in Normal Individuals

There is a considerable body of literature on the prevalence of HPV in normal hosts. Detection of HPV in normal oral mucosa would suggest that not all HPV infections necessarily lead to carcinogenesis, and it would be important to identify the factors that lead to its ability to induce malignant transformation. However, due to the plethora of molecular techniques used for detection, a wide range of values in normal individuals has been reported, from 0% (Eike *et al.*, 1995; Cruz *et al.*, 1996; Mao *et al.*, 1996; Nielsen *et al.*, 1996; Bouda *et al.*, 2000; Sand *et al.*, 2000) up to 70% (Terai *et al.*, 1999) (see Table 1◆). It appears that even the technique one uses to sample oral mucosa affects the sensitivity of detection. In one study, up to 60% of normal volunteers had some form of HPV in their oral mucosa (43% with either type 16 or 18), though the detection rate varied depending on whether buccal scrapings, biopsy, or mouthwash was collected (Lawton *et al.*, 1992). A similar prevalence (43%) of HPV-16 was found in buccal swabs of a healthy population, though these individuals did not demonstrate HPV DNA in their peripheral lymphocytes (Jalal *et al.*, 1992). The finding of high-risk HPV in presumably normal individuals' mucosa implies that these individuals may have a dormant infection that could contribute to the development of oral cancer in the future (Sugerman and Shillitoe, 1997).

TABLE 1 HPV Prevalence in Normal Oral Cavity Mucosa

Study	Mode of Detection	HPV+*	%	Tumor Type
Maitland *et al.*, 1987	Southern blot	5/ 12	41.6	Normal control mucosa
Jalal *et al.*, 1992	HPV16-specific primers	21/ 48	43.8	Normal oral mucosa
Holladay and Gerald, 1993	E1 PCR	1/ 6	16.7	Normal control mucosa
Ostwald *et al.*, 1994	Consensus PCR	1/ 97	1	Normal control mucosa
Eike *et al.*, 1995	L1 consensus PCR	0/ 61	0	Normal oral mucosa
Cruz *et al.*, 1996	Consensus PCR	0/ 12	0	Normal control mucosa
Mao *et al.*, 1996	L1 consensus and E6/7 PCR	0/ 6	0	Normal control mucosa

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Nielsen *et al.*, 1996	ISH/HPV 16 PCR	0/ 20	0	Normal control mucosa
Lambropoulos *et al.*, 1997	HPV16-specific primers	4/169	2.4	Normal oral mucosa
Smith *et al.*, 1998	L1 consensus PCR	2/205	1	Normal control mucosa
Terai *et al.*, 1999	L1 consensus PCR	26/37	70.3	Normal oral mucosa in individuals with cutaneous warts
Bouda *et al.*, 2000	Nested consensus PCR	0/ 16	0	Normal control mucosa
Sand *et al.*, 2000	L1 consensus type specific	0/ 12	0	Normal control mucosa
Nagpal *et al.*, 2002	Consensus PCR	7/ 26	26.9	Normal control mucosa

* These values were taken specifically for HPV 16 and/or HPV 18 when possible.

The more recent studies involving larger sample sizes (> 100) have reported a lower (1-2%) prevalence in normal individuals (Lambropoulos *et al.*, 1997; Smith *et al.*, 1998). Both of these latter studies utilized PCR, theoretically one of the most sensitive assays for HPV detection. Using similar techniques, investigators conducting a recent study in India in betel nut users found a detection rate of 27% (Nagpal *et al.*, 2002), raising the possibility that there are geographic, exposure-related, or other behavioral influences at play in individuals with normal oral mucosa.

Thus, normal individuals appear to have a wide range of reported prevalence rates which are likely dependent upon the different assays used for detection. It is possible that there are some geographical biases and that HPV is endemic in certain parts of the world. However, more recent, large studies indicate that the prevalence of HPV in normal oral mucosa is quite low (Smith *et al.*, 1998; Lambropoulos *et al.*, 1997).

(IV) Epidemiologic Support

A reasonable mechanistic link between HPV infection and oral cavity carcinogenesis is suggested by epidemiologic evidence, with odds ratios ranging between 0.5 and 6.2. One of the first case-control studies identified HPV-16 in various head and neck squamous carcinomas (HNSC), whereas none of the control group in matched anatomic sites harbored the virus (Brandsma and Abramson, 1989). A more recent case-control study examined the difference between an oral cancer group and a control group and demonstrated a higher risk of HPV infection in the oral cancer group (OR 3.70) after adjustment for age, smoking, and alcohol use (Smith *et al.*, 2000). Other case-control studies have also identified HPV-16 as a risk for the development of oral cancer (OR 6.2) (Maden *et al.*, 1992) and HNSC overall (OR 4.32) (Nishioka *et al.*, 1999).

In a landmark study, researchers examined a cohort of 900,000 individuals from Norway, Finland, and Sweden for HPV and the development of head and neck squamous carcinoma, while adjusting for smoking status by serum cotinine levels (Mork *et al.*, 2001). In this study, HPV status was ascertained in all patients by seropositive antibody status, and 160 of the 292 samples of head and neck cancer were tested with consensus and type-specific PCR. Of note, the investigators discovered that the mean time between serologic conversion and a diagnosis of cancer was 9.4 years, implying that there is a cause-and-effect relationship between HPV and cancer development. Overall, the adjusted odds ratio for development of HNSC in the setting of HPV 16 seropositivity was 2.2. Other types of HPV did not demonstrate an increased risk of HNSC development. This number increased to 14.4 and 20.7 in oropharyngeal and base-of-tongue tumors. respectively. Oral cavity carcinomas were also separated out by subsite: The odds ratio for lip lesions was 0.5 (95% CI = 0.1-2.1); for the tongue, it was 2.8 (95% CI = 1.2-6.6); for the floor of mouth, it was 0; and for the other areas, it was 3.6 (95% CI = 0.5-26.3). These particular ratios are less impressive than the oropharyngeal values obtained, with only the tongue having a statistically significant elevation.

Therefore, a link between head and neck cancer and oropharyngeal HPV infection (specifically type 16) was drawn with the use of large-scale epidemiologic data. While these values may seem impressive, they should be put into the context that the odds ratio of the development of cervical

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

squamous cell carcinoma in the setting of HPV infection is 74 (Munoz, 2000). Furthermore, while the population studied was quite large, the actual number of cases of head and neck malignancy in the cohort was quite low (309 cases identified, 228 specimens analyzed for HPV). It is also interesting to note that the odds ratios of true oral cavity malignancies were rather low.

Large-scale epidemiologic data were also reviewed in patients with known HPV-associated anogenital carcinoma and their risk of subsequent development of HNSC. Analysis of Surveillance, Epidemiology, and End Results (SEER) data indicated a relative risk of 2.3 for oral cavity cancer and a relative risk of 4.3 for the development of tonsillar cancer (Frisch and Biggar, 1999) in these patients. These findings support the role of HPV in oral cavity carcinoma, though the odds ratios are modest.

(V) HPV in Pre-malignant Lesions

It has been well-established that head and neck cancer follows a genetic progression from normal to invasive disease. Early lesions begin with dysplasia and subsequently undergo an accumulation of genetic alterations leading to the development of malignancy (Califano *et al.*, 1996). Given these findings, many investigators have studied the prevalence of HPV in these early lesions, hoping to find a similar progression of HPV prevalence with malignant disease. An increasing prevalence of HPV in pre-malignant lesions would suggest that it does play a role in malignant transformation. Again, the studies have reported varied results due to the differences in samples and molecular assays utilized, from 0% (Zeuss *et al.*, 1991; Fouret *et al.*, 1995) to 85% (Bouda *et al.*, 2000) (see Table 2◆). Pre-malignant lesions offer an additional level of complexity in cross-comparison of studies, since many of the terms used to describe these lesions have changed over the years. Currently, dysplasia (mild, moderate, and severe) and carcinoma *in situ* are recognized as pre-cancerous, whereas many of the other terms commonly used—such as leukoplakias, erythroplakia, lichen planus, etc.—describe a gross morphology, not necessarily a histologic alteration. Therefore, we have attempted to focus on those studies that have defined lesions by histopathologic diagnosis.

TABLE 2 HPV Prevalence in Oral Cavity Pre-malignant Lesions

Study	Mode of Detection	HPV+*	%	Lesion Type
Maitland *et al.*, 1987	SB using HPV 16 probe	16/21	28.6	Dysplasia keratosis hyperplasia lichen planus
Gassenmaier and Hornstein, 1988	ISH	19/103	18.4	Dysplasia
Syrjanen *et al.*, 1988a	ISH 6, 11, 13, 16, 18, 30	6/ 22	27.3	Dysplasia CIS
Greer *et al.*, 1990	ISH 6, 11, 16, 18, 31, 33, 35	5/190	2.6	Leukoplakia dysplasia
Shroyer and Greer, 1991	E6 HPV-16 PCR/ISH	7/ 48	14.6	Dysplasia hyperplasia keratosis
Zeuss *et al.*, 1991	ISH 6/11, 16/18, 31/33/35	0/20	0	Dysplasia CIS
Holladay and Gerald, 1993	E1 PCR	13/45	28.9	CIS dysplasia inflammation hyperplasia
Fouret *et al.*, 1995	E6 consensus PCR	0/ 3	0	Dysplasia
Mao *et al.*, 1996	L1 consensus and E6/7 PCR	8/23	34.8	Dysplasia CIS
Nielsen *et al.*, 1996	ISH/ HPV 16 PCR, SB PCR	20/49	40.8	Dyplasia leukoplakias
Wen *et al.*, 1997	E6 HPV 16/18 PCR	5/17	29.4	Papilloma leukoplakias lichen planus
D'Costa *et al.*, 1998	L1 consensus PCR	27/80	33.8	Leukoplakias lichen planus submucous fibrosis melanoplakia
Elamin *et al.*, 1998	Nested L1 PCR	4/12	33.3	Dysplasia
Matzow *et al.*, 1998	Consensus PCR	1/ 5	20	CIS hyperplasia

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Bouda *et al.*, 2000	Nested consensus PCR	29/34	85.2	Hyperplasia dysplasia
Sand *et al.*, 2000	L1 consensus type-specific	8/29	27.6	Lichen planus leukoplakias
Ha *et al.*, 2002	Quantitative PCR	1/102	1.0	Dysplasia CIS
* These values were taken specifically for HPV 16 and/or HPV 18 when possible.				

A recent study using quantitative PCR examined over 100 pre-malignant oral cavity lesions and found a prevalence of 1.0% (Ha *et al.*, 2002). This particular study is of interest in that the quantitative assay allowed the authors to evaluate the amount of HPV 16 or 18 DNA present in any given sample. The authors proposed that clonal, neoplastic proliferations should have at least one HPV copy *per* genome to be consistent with a role as an etiologic agent in malignant progression. Therefore, small quantities or contamination that would otherwise be called positive on routine PCR could be excluded on this basis. New techniques such as quantitative PCR have found that HPV is present in only a very small minority of oral pre-malignant lesions.

(VI) HPV in Oral Cavity Malignancies

The majority of literature on oral cavity lesions and HPV has focused on squamous cell carcinomas. Many studies have been performed with a wide array of molecular assays described earlier. Once again, the data range from 0% (Zeuss *et al.*, 1991; Matzow *et al.*, 1998; Miguel *et al.*, 1998) to 100% (Uobe *et al.*, 2001) (see Table 3✦). Many other reviews have looked at these trends to 'tease out' factors that account for the differences between and among studies.

TABLE 3 HPV Prevalence in Oral Cavity Carcinoma Studies

Study*	Mode of Detection	HPV+**	%	Tumor Type
de Villiers *et al.*, 1985	Southern blot	2/ 7	28.5	SCC
Maitland *et al.*, 1987	Southern blot	7/ 15	46.7	SCC
Gassenmaier and Hornstein, 1988	ISH	16/ 68	23.5	SCC
Syrjanen *et al.*, 1988b	ISH 6, 11, 13, 16, 18, 30	6/ 51	11.8	SCC
Greer *et al.*, 1990)	ISH 6, 11, 16, 18, 31, 33, 35	6/ 70	8.6	SCC
Shroyer and Greer, 1991	E6 HPV-16 PCR/ISH	1/ 13	7.7	SCC
Watts *et al.*, 1991	Southern blot	11/ 23 by SB	47.8	SCC
	E6 type-specific PCR	11/ 14 by PCR	78.6	
Yeudall and Campo, 1991	Southern blot (16&18), type-specific PCR (16/18)	2/ 39 by SB	5.1	SCC
		18/ 39 by PCR	46.2	
Zeuss *et al.*, 1991	ISH 6/11, 16/18, 31/33/35	0/ 15	0	SCC
Shindoh *et al.*, 1992	PCR and dot-blot	8/ 24	33.3	SCC
Holladay and Gerald, 1993	E1 PCR	7/ 39	17.9	SCC
Ostwald *et al.*, 1994	Consensus PCR	16/ 26	61.5	SCC
Balaram *et al.*, 1995	Consensus PCR	67/ 91	73.6	SCC
Fouret *et al.*, 1995	E6 consensus PCR	2/ 21	9.5	SCC
Cruz *et al.*, 1996	Consensus PCR	19/ 35	54.3	SCC
Mao *et al.*, 1996	L1 consensus and E6/7 PCR	12/ 41	29.3	SCC
Paz *et al.*, 1997	L1 and E1 consensus	10/ 71	14.1	SCC
Wen *et al.*, 1997	E6 HPV16/18 PCR	14/ 45	31.1	SCC
D'Costa *et al.*, 1998	L1 consensus PCR	15/100	15	SCC
Elamin *et al.*, 1998	Nested L1 PCR	14/ 28	50	SCC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Matzow *et al.*, 1998	Consensus PCR	0/ 30	0	SCC
Miguel *et al.*, 1998	L1 consensus PCR	0/ 16	0	SCC
Mineta *et al.*, 1998	PCR	3/ 14	7.1	SCC
Schwartz *et al.*, 1998	L1 consensus and E6 PCR	22/193	11.4	SCC
Smith *et al.*, 1998	L1 consensus PCR	8/ 93	8.6	SCC
Pintos *et al.*, 1999	L1 consensus PCR	3/ 29	10.3	SCC
Bouda *et al.*, 2000	Nested consensus PCR	17/ 19	89.5	SCC
Gillison *et al.*, 2000	L1 consensus, type-specific PCR 16/18, Southern blot, ISH	10/ 84	11.9	SCC
Sand *et al.*, 2000	L1 consensus, type-specific	3/ 24	12.5	SCC
Shima *et al.*, 2000	E6/7 consensus PCR	34/ 46	73.9	SCC
Klussmann *et al.*, 2001	Nested PCR	4/ 22	18.2	SCC
Uobe *et al.*, 2001	L1 *in situ* PCR	20/ 20 by ISPCR	100	SCC
	ISH	0/ 20 by ISH	0	
Ha *et al.*, 2002	Quantitative PCR	1/ 34	2.9	SCC
Nagpal *et al.*, 2002	Consensus PCR	37/110	33.6	SCC
Ringstrom *et al.*, 2002	Consensus PCR	2/ 41	4.9	SCC
Ritchie *et al.*, 2003	Consensus PCR	10/ 94	10.6	92% SCC
* These studies cited have samples solely from primary tumor, not cell line, DNA.				
** These values were taken specifically for HPV 16 and/or HPV 18 when possible.				

In a large review of the literature examining the role of HPV in oral lesions, HPV was detected in 13.5% of normal mucosa and 26.2% of squamous carcinoma (Miller and White, 1996). The authors noted that DNA was more likely to be detected in fresh-frozen than in paraffin-embedded samples, and that the mode of detection was a significant factor in the prevalence reported in various studies (Miller and White, 1996). Another large review of head and neck samples noted that the HPV prevalence in HNSC as detected by PCR was 34.5%, by ISH 15.8%, and by Southern blot 24.5% (McKaig *et al.*, 1998). Thus, it is no surprise that, overall, PCR exhibits a higher sensitivity and ability to detect the presence of HPV. However, PCR-positive lesions may be a result of minute contamination or subclonal infection that does not necessarily indicate a real contribution to carcinogenesis.

The larger studies using PCR detected HPV infection rates of approximately 10-15%. Thus, even when the most sensitive of techniques is used, there is still a low rate of detection of HPV in oral cavity malignancies. Moreover, the significance of HPV DNA presence in the progression to malignancy is still unclear. It *is* clear, however, that oral carcinoma is different from cervical cancer, where HPV infection is necessary for disease development.

This current review highlights the same challenges identified in previous review articles: diverse patient populations with likely different rates of endemic infection, different molecular assays used by a variety of authors, a lack of understanding of the link between HPV and carcinogenesis in the integrated *vs.* the non-integrated state, and an unknown link between HPV DNA presence and activity. While many new studies have proposed epidemiologic, serologic, molecular, and mechanistic roles of HPV and its contribution to oral cancer, there continue to be debate and a wide range of reported prevalence in normal individuals and those with pre-malignant and malignant lesions.

In addition to the technical aspects of HPV detection, the simple nomenclature regarding anatomic locations of oral cavity *vs.* oropharyngeal lesions is often unclear. The literature clearly supports the idea that oropharyngeal cancers are more likely to have HPV than other head and neck tumors.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Anatomically, the oral cavity and oropharyngeal border is the posterior 1/3 of the oral tongue, which is clinically difficult to delineate in many cases. Thus, there may be a significant portion of oropharyngeal tumors that are included in the oral cavity group, falsely elevating the number of HPV-positive samples, or *vice versa*.

Summary

HPV has been shown to be a significant carcinogen in cervical cancer, but the significance of human papillomavirus' contribution to oral squamous cell carcinoma has been studied for several decades and remains debated. Putative molecular mechanisms have been identified that clearly demonstrate its ability to disrupt key cellular elements responsible for the regulation of cell division and apoptosis. However, while epidemiologic and molecular data provide some evidence of high-risk HPV presence in oral pre-malignant and malignant lesions, it likely exists in only a small minority of cases. Thus, HPV may be a contributing factor in a subset of oral malignancies but is not a necessity in all cases, as it is in cervical cancer. Further studies using newer molecular techniques will shed light on this controversial topic and clarify the prevalence of HPV DNA in these samples and, more importantly, elucidate the significance of HPV infection in the oral cavity.

REFERENCES

1. Baker CC, Phelps WC, Lindgren V, Braun MJ, Gonda MA, Howley PM (1987). Structural and transcriptional analysis of human papillomavirus type 16 sequences in cervical carcinoma cell lines. *J Virol* 61:962–971.[Abstract/Free Full Text]
2. Balaram P, Nalinakumari KR, Abraham E, Balan A, Hareendran NK, Bernard HU, *et al.* (1995). Human papillomaviruses in 91 oral cancers from Indian betel quid chewers—high prevalence and multiplicity of infections. *Int J Cancer* 61:450–454.[Medline]
3. Bouda M, Gorgoulis VG, Kastrinakis NG, Giannoudis A, Tsoli E, Danassi-Afentaki D, *et al.* (2000). "High risk" HPV types are frequently detected in potentially malignant and malignant oral lesions, but not in normal oral mucosa. *Mod Pathol* 13:644–653.[Medline]
4. Boyer SN, Wazer DE, Band V (1996). E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res* 56:4620–4624.[Abstract/Free Full Text]
5. Brandsma JL, Abramson AL (1989). Association of papillomavirus with cancers of the head and neck. *Arch Otolaryngol Head Neck Surg* 115:621–625.[Abstract]
6. Brandsma J, Burk RD, Lancaster WD, Pfister H, Schiffman MH (1989). Inter-laboratory variation as an explanation for varying prevalence estimates of human papillomavirus infection. *Int J Cancer* 43:260–262.[Medline]
7. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, *et al.* (1996). Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Res* 56:2488–2492.[Abstract/Free Full Text]
8. Carter JJ, Koutsky LA, Wipf GC, Christensen ND, Lee SK, Kuypers J, *et al.* (1996). The natural history of human papillomavirus type 16 capsid antibodies among a cohort of university women. *J Infect Dis* 174:927–936.[Medline]
9. Combita AL, Bravo MM, Touze A, Orozco O, Coursaget P (2002). Serologic response to human oncogenic papillomavirus types 16, 18, 31, 33, 39, 58 and 59 virus-like particles in Colombian women with invasive cervical cancer. *Int J Cancer* 97:796–803.[Medline]
10. Cruz IB, Snijders PJ, Steenbergen RD, Meijer CJ, Snow GB, Walboomers JM, *et al.* (1996). Age-dependence of human papillomavirus DNA presence in oral squamous cell carcinomas. *Eur J Cancer B Oral Oncol* 32B:55–62.[Medline]
11. D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR (1998). Detection of HPV-16 genome in human oral cancers and potentially malignant lesions from India. *Oral Oncol* 34:413–420.[Medline]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

12. de Villiers EM, Weidauer H, Otto H, zur Hausen H (1985). Papillomavirus DNA in human tongue carcinomas. *Int J Cancer* 36:575–578.[Medline]
13. Dyson N, Howley PM, Munger K, Harlow E (1989). The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 243:934–937.[Abstract/Free Full Text]
14. Eike A, Buchwald C, Rolighed J, Lindeberg H (1995). Human papillomavirus (HPV) is rarely present in normal oral and nasal mucosa. *Clin Otolaryngol* 20:171–173.[Medline]
15. Elamin F, Steingrimsdottir H, Wanakulasuriya S, Johnson N, Tavassoli M (1998). Prevalence of human papillomavirus infection in premalignant and malignant lesions of the oral cavity in UK subjects: a novel method of detection. *Oral Oncol* 34:191–197.[Medline]
16. Evander M, Wadell G (1991). A general primer pair for amplification and detection of genital human papillomavirus types. *J Virol Methods* 31:239–250.[Medline]
17. Evander M, Edlund K, Gustafsson A, Jonsson M, Karlsson R, Rylander E, *et al.* (1995). Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis* 171:1026–1030.[Medline]
18. Fouret P, Martin F, Flahault A, Saint-Guily JL (1995). Human papillomavirus infection in the malignant and premalignant head and neck epithelium. *Diagn Mol Pathol* 4:122–127.[Medline]
19. Frazer IH, Leonard JH, Schonrock J, Wright RG, Kearsley JH (1993). HPV DNA in oropharyngeal squamous cell cancers: comparison of results from four DNA detection methods. *Pathology* 25:138–143.[Medline]
20. Frisch M, Biggar RJ (1999). Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas. *Lancet* 354:1442–1443.[Medline]
21. Gassenmaier A, Hornstein OP (1988). Presence of human papillomavirus DNA in benign and precancerous oral leukoplakias and squamous cell carcinomas. *Dermatologica* 176:224–233.[Medline]
22. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, *et al.* (2000). Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 92:709–720.[Abstract/Free Full Text]
23. Greer RO, Eversole LR, Crosby LK (1990). Detection of human papillomavirus-genomic DNA in oral epithelial dysplasias, oral smokeless tobacco-associated leukoplakias, and epithelial malignancies. *J Oral Maxillofac Surg* 48:1201–1205.[Medline]
24. Gregoire L, Arella M, Campione-Piccardo J, Lancaster WD (1989). Amplification of human papillomavirus DNA sequences by using conserved primers. *J Clin Microbiol* 27:2660–2665.[Abstract/Free Full Text]
25. Ha PK, Pai SI, Westra WH, Gillison ML, Tong BC, Sidransky D, *et al.* (2002). Real-time quantitative PCR demonstrates low prevalence of human papillomavirus type 16 in premalignant and malignant lesions of the oral cavity. *Clin Cancer Res* 8:1203–1209.[Abstract/Free Full Text]
26. Hashida T, Yasumoto S (1991). Induction of chromosome abnormalities in mouse and human epidermal keratinocytes by the human papillomavirus type 16 E7 oncogene. *J Gen Virol* 72:1569–1577.[Abstract/Free Full Text]
27. Havre PA, Yuan J, Hedrick L, Cho KR, Glazer PM (1995). p53 inactivation by HPV16 E6 results in increased mutagenesis in human cells. *Cancer Res* 55:4420–4424.[Abstract/Free Full Text]
28. Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, *et al.* (1994). Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 169:235–240.[Medline]
29. Holladay EB, Gerald WL (1993). Viral gene detection in oral neoplasms using the polymerase chain reaction. *Am J Clin Pathol* 100:36–40.[Medline]
30. Hollstein M, Sidransky D, Vogelstein B, Harris CC (1991). p53 mutations in human cancers. *Science* 253:49–53.[Abstract/Free Full Text]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

31. Jalal H, Sanders CM, Prime SS, Scully C, Maitland NJ (1992). Detection of human papilloma virus type 16 DNA in oral squames from normal young adults. *J Oral Pathol Med* 21:465–470.[Medline]
32. Jochmus-Kudielka I, Schneider A, Braun R, Kimmig R, Koldovsky U, Schneweis KE, *et al.* (1989). Antibodies against the human papillomavirus type 16 early proteins in human sera: correlation of anti-E7 reactivity with cervical cancer. *J Natl Cancer Inst* 81:1698–1704.[Abstract/Free Full Text]
33. Karlsen F, Kalantari M, Jenkins A, Pettersen E, Kristensen G, Holm R, *et al.* (1996). Use of multiple PCR primer sets for optimal detection of human papillomavirus. *J Clin Microbiol* 34:2095–2100.[Abstract]
34. Kessis TD, Slebos RJ, Han SM, Shah K, Bosch XF, Munoz N, *et al.* (1993a). p53 gene mutations and MDM2 amplification are uncommon in primary carcinomas of the uterine cervix. *Am J Pathol* 143:1398–1405.[Abstract]
35. Kessis TD, Slebos RJ, Nelson WG, Kastan MB, Plunkett BS, Han SM, *et al.* (1993b). Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. *Proc Natl Acad Sci USA* 90:3988–3992.[Abstract/Free Full Text]
36. Kirnbauer R, Hubbert NL, Wheeler CM, Becker TM, Lowy DR, Schiller JT (1994). A virus-like particle enzyme-linked immunosorbent assay detects serum antibodies in a majority of women infected with human papillomavirus type 16. *J Natl Cancer Inst* 86:494–499.[Abstract/Free Full Text]
37. Klussmann JP, Weissenborn SJ, Wieland U, Dries V, Kolligs J, Jungehuelsing M, *et al.* (2001). Prevalence distribution and viral load of human papillomavirus 16 DNA in tonsillar carcinomas. *Cancer* 92:2875–2884.[Medline]
38. Lambropoulos AF, Dimitrakopoulos J, Frangoulides E, Katopodi R, Kotsis A, Karakasis D (1997). Incidence of human papillomavirus 6, 11, 16, 18 and 33 in normal oral mucosa of a Greek population. *Eur J Oral Sci* 105:294–297.[Medline]
39. Lawton G, Thomas S, Schonrock J, Monsour F, Frazer I (1992). Human papillomaviruses in normal oral mucosa: a comparison of methods for sample collection. *J Oral Pathol Med* 21:265–269.[Medline]
40. Lehn H, Krieg P, Sauer G (1985). Papillomavirus genomes in human cervical tumors: analysis of their transcriptional activity. *Proc Natl Acad Sci USA* 82:5540–5544.[Abstract/Free Full Text]
41. Levine AJ (1990). The p53 protein and its interactions with the oncogene products of the small DNA tumor viruses. *Virology* 177:419–426.[Medline]
42. Liu X, Han S, Baluda MA, Park NH (1997). HPV-16 oncogenes E6 and E7 are mutagenic in normal human oral keratinocytes. *Oncogene* 14:2347–2353.[Medline]
43. Loning T, Ikenberg H, Becker J, Gissmann L, Hoepfer I, zur Hausen H (1985). Analysis of oral papillomas, leukoplakias, and invasive carcinomas for human papillomavirus type related DNA. *J Invest Dermatol* 84:417–420.[Medline]
44. Maden C, Beckmann AM, Thomas DB, McKnight B, Sherman KJ, Ashley RL, *et al.* (1992). Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol* 135:1093–1102.[Abstract/Free Full Text]
45. Maitland NJ, Cox MF, Lynas C, Prime SS, Meanwell CA, Scully C (1987). Detection of human papillomavirus DNA in biopsies of human oral tissue. *Br J Cancer* 56:245–250.[Medline]
46. Maitland NJ, Bromidge T, Cox MF, Crane IJ, Prime SS, Scully C (1989). Detection of human papillomavirus genes in human oral tissue biopsies and cultures by polymerase chain reaction. *Br J Cancer* 59:698–703.[Medline]
47. Mao EJ, Schwartz SM, Daling JR, Oda D, Tickman L, Beckmann AM (1996). Human papilloma viruses and p53 mutations in normal pre-malignant and malignant oral epithelia. *Int J Cancer* 69:152–158.[Medline]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

48. Matzow T, Boysen M, Kalantari M, Johansson B, Hagmar B (1998). Low detection rate of HPV in oral and laryngeal carcinomas. *Acta Oncol* 37:73–76.[Medline]
49. McKaig RG, Baric RS, Olshan AF (1998). Human papillomavirus and head and neck cancer: epidemiology and molecular biology. *Head Neck* 20:250–265.[Medline]
50. Miguel RE, Villa LL, Cordeiro AC, Prado JC, Sobrinho JS, Kowalski LP (1998). Low prevalence of human papillomavirus in a geographic region with a high incidence of head and neck cancer. *Am J Surg* 176:428–429.[Medline]
51. Miller CS, White DK (1996). Human papillomavirus expression in oral mucosa premalignant conditions and squamous cell carcinoma: a retrospective review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 82:57–68.[Medline]
52. Mineta H, Ogino T, Amano HM, Ohkawa Y, Araki K, Takebayashi S, *et al.* (1998). Human papilloma virus (HPV) type 16 and 18 detected in head and neck squamous cell carcinoma. *Anticancer Res* 18:4765–4768.[Medline]
53. Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P, *et al.* (2001). Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 344:1125–1131.[Abstract/Free Full Text]
54. Munger K, Phelps WC, Bubb V, Howley PM, Schlegel R (1989). The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. *J Virol* 63:4417–4421.[Abstract/Free Full Text]
55. Munoz N (2000). Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol* 19:1–5.[Medline]
56. Nagpal JK, Patnaik S, Das BR (2002). Prevalence of high-risk human papilloma virus types and its association with P53 codon 72 polymorphism in tobacco addicted oral squamous cell carcinoma (OSCC) patients of Eastern India. *Int J Cancer* 97:649–653.[Medline]
57. Nielsen H, Norrild B, Vedtofte P, Praetorius F, Reibel J, Holmstrup P (1996). Human papillomavirus in oral premalignant lesions. *Eur J Cancer B Oral Oncol* 32(B):264–270.
58. Nishioka S, Fukushima K, Nishizaki K, Gunduz M, Tominaga S, Fukazawa M, *et al.* (1999). Human papillomavirus as a risk factor for head and neck cancers—a case-control study. *Acta Otolaryngol Suppl* 540:77–80.[Medline]
59. Oda D, Bigler L, Lee P, Blanton R (1996). HPV immortalization of human oral epithelial cells: a model for carcinogenesis. *Exp Cell Res* 226:164–169.[Medline]
60. Ostwald C, Muller P, Barten M, Rutsatz K, Sonnenburg M, Milde-Langosch K, *et al.* (1994). Human papillomavirus DNA in oral squamous cell carcinomas and normal mucosa. *J Oral Pathol Med* 23:220–225.[Medline]
61. Park NH, Min BM, Li SL, Huang MZ, Cherick HM, Doniger J (1991). Immortalization of normal human oral keratinocytes with type 16 human papillomavirus. *Carcinogenesis* 12:1627–1631.[Abstract/Free Full Text]
62. Paz IB, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP (1997). Human papillomavirus (HPV) in head and neck cancer. An association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer* 79:595–604.[Medline]
63. Pintos J, Franco EL, Black MJ, Bergeron J, Arella M (1999). Human papillomavirus and prognoses of patients with cancers of the upper aerodigestive tract. *Cancer* 85:1903–1909.[Medline]
64. Resnick RM, Cornelissen MT, Wright DK, Eichinger GH, Fox HS, ter Schegget J, *et al.* (1990). Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers. *J Natl Cancer Inst* 82:1477–1484.[Abstract/Free Full Text]
65. Ringstrom E, Peters E, Hasegawa M, Posner M, Liu M, Kelsey KT (2002). Human papillomavirus type 16 and squamous cell carcinoma of the head and neck. *Clin Cancer Res* 8:3187–3192.[Abstract/Free Full Text]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

66. Ritchie JM, Smith EM, Summersgill KF, Hoffman HT, Wang D, Klussmann JP, *et al.* (2003). Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. *Int J Cancer* 104:336–344.[Medline]
67. Sand L, Jalouli J, Larsson PA, Hirsch JM (2000). Human papilloma viruses in oral lesions. *Anticancer Res* 20:1183–1188.[Medline]
68. Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM (1990). The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell* 63:1129–1136.[Medline]
69. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM (1993). The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. *Cell* 75:495–505.[Medline]
70. Schiffman MH (1992). Validation of hybridization assays: correlation of filter in situ dot blot and PCR with Southern blot. *IARC Sci Publ* 119:169–179.
71. Schneider-Gadicke A, Schwarz E (1986). Different human cervical carcinoma cell lines show similar transcription patterns of human papillomavirus type 18 early genes. *EMBO J* 5:2285–2292.[Medline]
72. Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, *et al.* (1998). Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 90:1626–1636.[Abstract/Free Full Text]
73. Schwarz E, Freese UK, Gissmann L, Mayer W, Roggenbuck B, Stremlau A, *et al.* (1985). Structure and transcription of human papillomavirus sequences in cervical carcinoma cells. *Nature* 314:111–114.[Medline]
74. Shibata DK, Arnheim N, Martin WJ (1988). Detection of human papilloma virus in paraffin-embedded tissue using the polymerase chain reaction. *J Exp Med* 167:225–230.[Abstract/Free Full Text]
75. Shima K, Kobayashi I, Saito I, Kiyoshima T, Matsuo K, Ozeki S, *et al.* (2000). Incidence of human papillomavirus 16 and 18 infection and p53 mutation in patients with oral squamous cell carcinoma in Japan. *Br J Oral Maxillofac Surg* 38:445–450.[Medline]
76. Shindoh M, Sawada Y, Kohgo T, Amemiya A, Fujinaga K (1992). Detection of human papillomavirus DNA sequences in tongue squamous-cell carcinoma utilizing the polymerase chain reaction method. *Int J Cancer* 50:167–171.[Medline]
77. Shope R (1933). Infectious papillomatosis of rabbits. *J Exp Med* 58:607–624.[Abstract]
78. Shroyer KR, Greer RO (1991). Detection of human papillomavirus DNA by in situ DNA hybridization and polymerase chain reaction in premalignant and malignant oral lesions. *Oral Surg Oral Med Oral Pathol* 71:708–713.[Medline]
79. Smith EM, Hoffman HT, Summersgill KS, Kirchner HL, Turek LP, Haugen TH (1998). Human papillomavirus and risk of oral cancer. *Laryngoscope* 108:1098–1103.[Medline]
80. Smith EM, Summersgill KF, Allen J, Hoffman HT, McCulloch T, Turek LP, *et al.* (2000). Human papillomavirus and risk of laryngeal cancer. *Ann Otol Rhinol Laryngol* 109:1069–1076.[Medline]
81. Snijders PJ, Meijer CJ, Walboomers JM (1991). Degenerate primers based on highly conserved regions of amino acid sequence in papillomaviruses can be used in a generalized polymerase chain reaction to detect productive human papillomavirus infection. *J Gen Virol* 72:2781–2786.[Abstract/Free Full Text]
82. Stoler MH, Wolinsky SM, Whitbeck A, Broker TR, Chow LT (1989). Differentiation-linked human papillomavirus types 6 and 11 transcription in genital condylomata revealed by in situ hybridization with message-specific RNA probes. *Virology* 172:331–340.[Medline]
83. Sugerman PB, Shillitoe EJ (1997). The high risk human papillomaviruses and oral cancer: evidence for and against a causal relationship. *Oral Dis* 3:130–147.[Medline]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

84. Syrjanen SM (1990). Basic concepts and practical applications of recombinant DNA techniques in detection of human papillomavirus (HPV) infection (review article). *APMIS* 98:95–110.[Medline]
85. Syrjanen K, Syrjanen S, Lamberg M, Pyrhonen S, Nuutinen J (1983). Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. *Int J Oral Surg* 12:418–424.[Medline]
86. Syrjanen S, Partanen P, Mantyjarvi R, Syrjanen K (1988a). Sensitivity of in situ hybridization techniques using biotin- and ^{35}S-labeled human papillomavirus (HPV) DNA probes. *J Virol Methods* 19:225–238.[Medline]
87. Syrjanen SM, Syrjanen KJ, Happonen RP (1988b). Human papillomavirus (HPV) DNA sequences in oral precancerous lesions and squamous cell carcinoma demonstrated by in situ hybridization. *J Oral Pathol* 17:273–278.[Medline]
88. Terai M, Hashimoto K, Yoda K, Sata T (1999). High prevalence of human papillomaviruses in the normal oral cavity of adults. *Oral Microbiol Immunol* 14:201–205.[Medline]
89. Tieben LM, ter Schegget J, Minnaar RP, Bouwes Bavinck JN, Berkhout RJ, Vermeer BJ, *et al.* (1993). Detection of cutaneous and genital HPV types in clinical samples by PCR using consensus primers. *J Virol Methods* 42:265–279.[Medline]
90. Uobe K, Masuno K, Fang YR, Li LJ, Wen YM, Ueda Y, *et al.* (2001). Detection of HPV in Japanese and Chinese oral carcinomas by in situ PCR. *Oral Oncol* 37:146–152.[Medline]
91. van Houten VM, Snijders PJ, van den Brekel MW, Kummer JA, Meijer CJ, van Leeuwen B, *et al.* (2001). Biological evidence that human papillomaviruses are etiologically involved in a subgroup of head and neck squamous cell carcinomas. *Int J Cancer* 93:232–235.[Medline]
92. von Knebel Doeberitz M, Oltersdorf T, Schwarz E, Gissmann L (1988). Correlation of modified human papilloma virus early gene expression with altered growth properties in C4-1 cervical carcinoma cells. *Cancer Res* 48:3780–3786.[Abstract/Free Full Text]
93. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189:12–19.[Medline]
94. Watts SL, Brewer EE, Fry TL (1991). Human papillomavirus DNA types in squamous cell carcinomas of the head and neck. *Oral Surg Oral Med Oral Pathol* 71:701–707.[Medline]
95. Wen S, Tsuji T, Li X, Mizugaki Y, Hayatsu Y, Shinozaki F (1997). Detection and analysis of human papillomavirus 16 and 18 homologous DNA sequences in oral lesions. *Anticancer Res* 17:307–311.[Medline]
96. Werness BA, Levine AJ, Howley PM (1990). Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 248:76–79.[Abstract/Free Full Text]
97. White AE, Livanos EM, Tlsty TD (1994). Differential disruption of genomic integrity and cell cycle regulation in normal human fibroblasts by the HPV oncoproteins. *Genes Dev* 8:666–677.[Abstract/Free Full Text]
98. Wilczynski SP, Lin BT, Xie Y, Paz IB (1998). Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. *Am J Pathol* 152:145–156.[Abstract]
99. Yeudall WA, Campo MS (1991). Human papillomavirus DNA in biopsies of oral tissues. *J Gen Virol* 72:173–176.[Abstract/Free Full Text]
100. Zeuss MS, Miller CS, White DK (1991). In situ hybridization analysis of human papillomavirus DNA in oral mucosal lesions. *Oral Surg Oral Med Oral Pathol* 71:714–720.[Medline]
101. Zumbach K, Hoffmann M, Kahn T, Bosch F, Gottschlich S, Gorogh T, *et al.* (2000). Antibodies against oncoproteins E6 and E7 of human papillomavirus types 16 and 18 in patients with head-and-neck squamous-cell carcinoma. *Int J Cancer* 85:815–818.[Medline]
102. zur Hausen H (1996). Papillomavirus infections—a major cause of human cancers. *Biochim Biophys Acta* 1288:F55–F78.[Medline]

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

103. zur Hausen H (2000). Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. *J Natl Cancer Inst* 92:690–698.[Abstract/Free Full Text]

* * * COMMUNICATION RESULT REPORT (MAR. 13. 2013 5:38PM) * * *

FAX HEADER 1:
FAX HEADER 2:

TRANSMITTED/STORED : MAR. 13. 2013 5:32PM FILE MODE	OPTION	ADDRESS	RESULT	PAGE
3753 MEMORY TX		+18553296725	OK	3/3

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) NO FACSIMILE CONNECTION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

March 13, 2013

Dr. Brian Pikkula
President & CTO
Forward Science LLC
2511 Wind Fall Lane
SUGAR LAND TX 77479

Re: K123169
Trade/Device Name: OralID™
Regulation Number: 21 CFR 872.6350
Regulation Name: Ultraviolet Detector
Regulatory Class: II
Product Code: NXV
Dated: February 6, 2013
Received: February 11, 2013

Dear Dr. Pikkula:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

5

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name Leah S. Royce, D.D.S.

Subject: 510(k) Number K123169

To: The Record

Please list CTS decision code SE

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)
☐ Hold (Additional Information or Telephone Hold).
☐ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.).

Not Substantially Equivalent (NSE) Codes

☐	NO	NSE for lack of predicate
☐	NI	NSE for new intended use
☐	NQ	NSE for new technology that raises new questions of safety and effectiveness
☐	NU	NSE for new intended use AND new technology raising new questions of safety and effectiveness
☐	NP	NSE for lack of performance data
☐	NS	NSE no response
☐	NL	NSE for lack of performance data AND no response
☐	NM	NSE pre-amendment device call for PMAs (515i)
☐	NC	NSE post-amendment device requires PMAs
☐	NH	NSE for new molecular entity requires PMA
☐	TR	NSE for transitional device

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	x	
510(k) Summary /510(k) Statement	*Attach Summary*	x	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	x	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		x
Does firm reference standards? (If yes, please attach form from http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf)		x	
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReg/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			x
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			x
Is this device intended for pediatric use only?			x
Is this a prescription device? (If both prescription & OTC, check both boxes.)		x	
Did the application include a completed FORM FDA 3674, Certification with Requirements of ClinicalTrials.gov Data Bank?			☒
Is clinical data necessary to support the review of this 510(k)? For United States-based clinical studies **only**: Did the application include a completed FORM FDA 3674, *Certification with Requirements of ClinicalTrials.gov Data Bank*? (If study was			☒

Rev. 2/29/12

C

conducted in the United States, and FORM FDA 3674 was not included or incomplete, then applicant must be contacted to obtain completed form.)			
Does this device include an Animal Tissue Source?			x
All Pediatric Patients age<=21			x
Neonate/Newborn (Birth to 28 days)			x
Infant (29 days -< 2 years old)			x
Child (2 years -< 12 years old)			x
Adolescent (12 years -< 18 years old)			x
Transitional Adolescent A (18 - <21 years old) Special considerations are being given to this group, different from adults age ≥ 21 (different device design or testing, different protocol procedures, etc.)			x
Transitional Adolescent B (18 -<= 21; No special considerations compared to adults => 21 years old)		x	
Nanotechnology			x
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		x

Regulation Number	**Class***	**Product Code**
21CFR8726350	II	NXV

(*If unclassified, see 510(k) Staff)

Additional Product Codes: EAQ, HQY

Review: Susan Runner -S 2013.03.13 10:59:50 -04'00' Mary S. Runner -S

(Branch Chief) (Branch Code) (Date)

Final Review: Kwame O. Ulmer 2013.03.13 14:47:39 -04'00' FDA

(Division Director) (Date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Premarket Notification [510(k)] Review
Traditional

K123169/S001

Date: March 13, 2013

To: The Record

Office: ODE

From: Leah S. Royce, D.D.S.

Division: DAGRID

510(k) Holder: Forward Science LLC

Device Name: Oral ID

Contact: Brian Pikkula, Ph.D.

Phone: 855-696-7254

Fax: 855-329-6725

Email: bpikkula@oralid.com

I. Purpose and Submission Summary

The 510(k) holder would like to introduce Oral ID into interstate commerce. Oral ID is a class II medical device regulated under 21CFR872.6350 as an ultraviolet detector, a device intended to provide a source of ultraviolet light used to identify otherwise invisible material such as dental plaque, present in or on teeth, under product code NXV. Oral ID accessories include photosensitive glasses (21 CFR 886.5859, HQY) which are class I exempt. The company identified the following predicate devices: VELscope Vx (K102083) and Dentlight Oral Exam Light Kit (K101140).

The submission included a medical device user fee cover sheet, a confirmation of payment document, a CDRH premarket review submission cover sheet, a table of contents, a 510(k) cover letter, general information, indications for use statement (IFUS), 510(k) Summary, Truthful and Accuracy Statement, Class III Summary and Certification statement, Financial Certification or Disclosure Statement, Declaration of Conformity, Executive Summary, Device description and specifications, substantial equivalence, proposed labeling, sterilization/shelf life statement, biocompatibility, software statement, electromagnetic compatibility/electrical summary, performance testing-bench, performance testing - animal, and performance testing - clinical statement that the submission included scientific abstracts and studies. The literature provided however was not determined to be directly relevant to the submission.

On October 31, 2012, an RTA checklist was completed and a request for additional information (AI) was sent by email to the company.

On November 7th, the company provided additional information in response to the RTA checklist and comments.
On February 8th, the company provided additional information labeled S001.
On February 19th, 20th, 27th, and March 7th, the sponsor provided additional information by email.
On February 22nd, a consult on optical and thermal safety was provided by Josh Pfeffer, PhD, CDRH/OSEL/DP

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	x		
Truthful and Accuracy Statement	x		
510(k) Summary or 510(k) Statement Summary	x		
Standards Data Report Form – Form 3654 1: No standard used - No Standards Form Required 2: Declaration of Conformity - Yes Standards Form Required 3: Standard but no declaration - Yes Standards Form Required	x		

(b) (4) [redacted]

In S001, the company provided SDRs for IEC 60601-1: Medical Electrical Equipment - Part 1; IEC 606011-1-2 Medical Electrical Equipment - Part 1-2:, IEC 62471 Photobiological Safety of lamps and lamp systems, ISO 13485: Medical Devices Quality Management systems; ISO 14971: Application of risk management to medical devices.
The 510(k) Summary included the IFUS, and a section on technological characteristics that contained marketing claims and no performance testing was included. FDA requested that the company remove the marketing claims, describe the performance testing and revise the substantial equivalence discussion.
On March 7th, the company provided a revised 510(k) Summary.

III. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		x	
Is the device an implant (implanted longer than 30 days)?		x	
Does the device design use software?		x	
Is the device sterile?		x	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?	x		

The submission stated that the device is a <175 mm length and <30 mm diameter hand-held, battery operated, oral illumination and examination light emitting diode (LED)-based optical source, with peak irradiation in the violet/blue region of the spectrum (b) (4) (b) (4) The light is used together with eyewear (filtered glasses accessories) to attenuate optical wavelengths of (b) (4) (b) (4)

A. The light:

1. Physical characteristics, material composition

(b) (4) (b) (4) The company stated that they had also updated the 510(k) Summary device description and provided the revised 510(k) Summary in Appendix B.

The submission stated the material composition of the device as (b) (4) (b) (4)

2. LED specification

The submission stated a range of wavelength for the device of (b) (4) (b) (4)

The submission provided information on the LED source in terms of spectral distribution and intensity, (b) (4) (b) (4)

3. Device operation

The submission stated that when healthy tissue is exposed to the blue light, the end user views

10

the tissue as green through the photosensitive glasses due to healthy tissue emitting fluorescence. The submission stated that under identical conditions, abnormal tissue will appear dark due to lack of fluorescence. (b) (4)
Principles of Operation, (b) (4)
(b) (4)
(b) (4) Reviewer analysis determined that this additional information was acceptable.
(b) (4)
Reviewer analysis of the response determined that the response was adequate.

B. The Accessories:
1. Eyewear: The submission stated that the eyewear is (b) (4)
(b) (4)
2. Batteries: The submission stated that 2 6.0 V primary lithium CR123A batteries power the LED, however there was no information on the battery life provided in the device description. In the labeling however, the submission states a cycle duty of 2 minutes on /2 minutes off. (see

bench performance testing section)

IV. Indications for Use

The submission provided the following IFUS:
Oral ID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.
Oral ID ™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence.
(b) (4)

Oral ID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the Oral ID blue light.

(b) (4)

(b) (4)

On February 19th and 20th, the sponsor provided additional clinical photographs on two patients, labeled patient C and patient D. Reviewer analysis determined that this additional information was acceptable(b) (4)
(b) (4)

On February 27th, the company provided a revised IFUS stated as follows:
OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

V. Predicate Device Comparison

The submission stated that the device differs from the predicate devices only in the power source. The submission device uses primary CR123A batteries, whereas the predicate devices use rechargeable batteries. All devices use batteries to power a high -intensity LED.
The submission included the following table: Comparison of Submission Device with Predicates:

12

	OralID Forward Science	VELscope Vx	Dentlight Oral Exam Light Kit
Submission number	K123169	K102083	K101140
Indications for use statement	Oral ID™ is intended to be used by qualified health-care providers to enhance the identification and visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia. Oral ID™ excites the tissue..... (b) (4) .....eyewear is reusable ...	VELscope Vx is intended to be used by a dentist or health-care provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia. VELscope Vx is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus ais in determining the appropriate margin for surgical excision.	Dentlight Oral Exam Light Kit is indicated for providing illumination to aid visualization during oral procedures and an adjunct to enhance the visualization for oral examination of mucosal abnormalities
Power source for LED	CR 123A primary lithium batteries	Rechargeable Lithium ion batteries	Rechargeable lithium battery
Method of operation	Direct visualization of fluorescent tissues	Direct visualization of fluorescent tissues	Direct visualization of fluorescent tissues
Wavelength Light intensity Projected light image	(b) (4)	400-460 nm blue light .75 W 4 cm at 10 cm distance	410nm violet light 530 nm green light 6000K (white) 30 – 75 mW/cm2

13

Clinical data		Photographs of a variety of oral mucosal lesions	Illumination and fluorescent image
Bench testing	Optical power mW	Spectral data…	Optical power testing
	Peak Wavelength nm		Optical wavelength
Cycle time recommended for use Operating temperature			Beam quality 5,10,20 seconds 0 – 35 degrees
Standards conformance	Referenced 60601		IEC 60601-1-2
Accessories	Two pair filtered glasses		

While the submission predicate device comparison provided a general, qualitative comparison of the subject and predicate devices, the company was asked to provide a quantitative comparison of the light sources -including total power, maximum local irradiance at clinically relevant distances, spectral distribution (including relative intensity of visible vs. ultraviolet radiation) and illumination uniformity - as well as eyepiece filtering characteristics of the subject and predicate devices.

In AI of February 27th, the company stated that the expected radiant flux of the OralID is (b) (4) (b) (4) The spectral distribution is provided in Appendix O in response to the telephone hold (FS-0236 - Evaluation of Optical Safety). The illumination uniformity of the subject device is provided. We do not have access to the predicate devices and thus cannot provide the detailed information requested. (b) (4) (b) (4)

(b) (4) K101140, (b) (4) (b) (4)

company was (b) (4) (b) (4)

(b) (4) The first in for the examination of the OralID Instructions for Use state,

"Conduct a thorough visual and manual oral examination, both extra-oral and intra-oral per the ADA guidelines." (b) (4)
(b) (4)

Review analysis of the response determined that the justification is adequate.

VI. Labeling

The submission provided draft labeling including the manufacturer address, name, contents, symbols with English translation, Directions for Use (DFU) with device description, intended uses identical to the IFUS, appropriate warnings regarding care and storage, and a caution not to look directly into the light. The labeling included selection of batteries but no information on expected battery life and power. (b) (4)
(b) (4)
(b) (4) This company was asked to clarify this statement, provide the IEC 60601 report, and to perform bench testing upon which to establish clear guidelines in the labeling for maximum use time and time required for the device to cool down.

In S001, the company stated that the report, (b) (4) addresses the power and wavelength of the LED light sources as a function of time; (b) (4)
(b) (4)

VII. Sterilization/Shelf Life/Reuse

The submission stated that sterilization and shelf life are not applicable. However the DFU included a section on maintenance, stating that the device "*should be cleaned and disinfected between each patient use. The external surfaces of the handpiece should be wiped down with a hospital grade surface disinfectant and a towlette or gauze…do not use disinfectants with alcohol content over 70%*". (b) (4)
(b) (4)

In S001, the company stated the DFU was updated in the Maintenance section, provided in
(b) (4)

VIII. Biocompatibility

(b) (4)

15

(b) (4)

[redacted]

biocompatibility testing is required at this time.

IX. Software

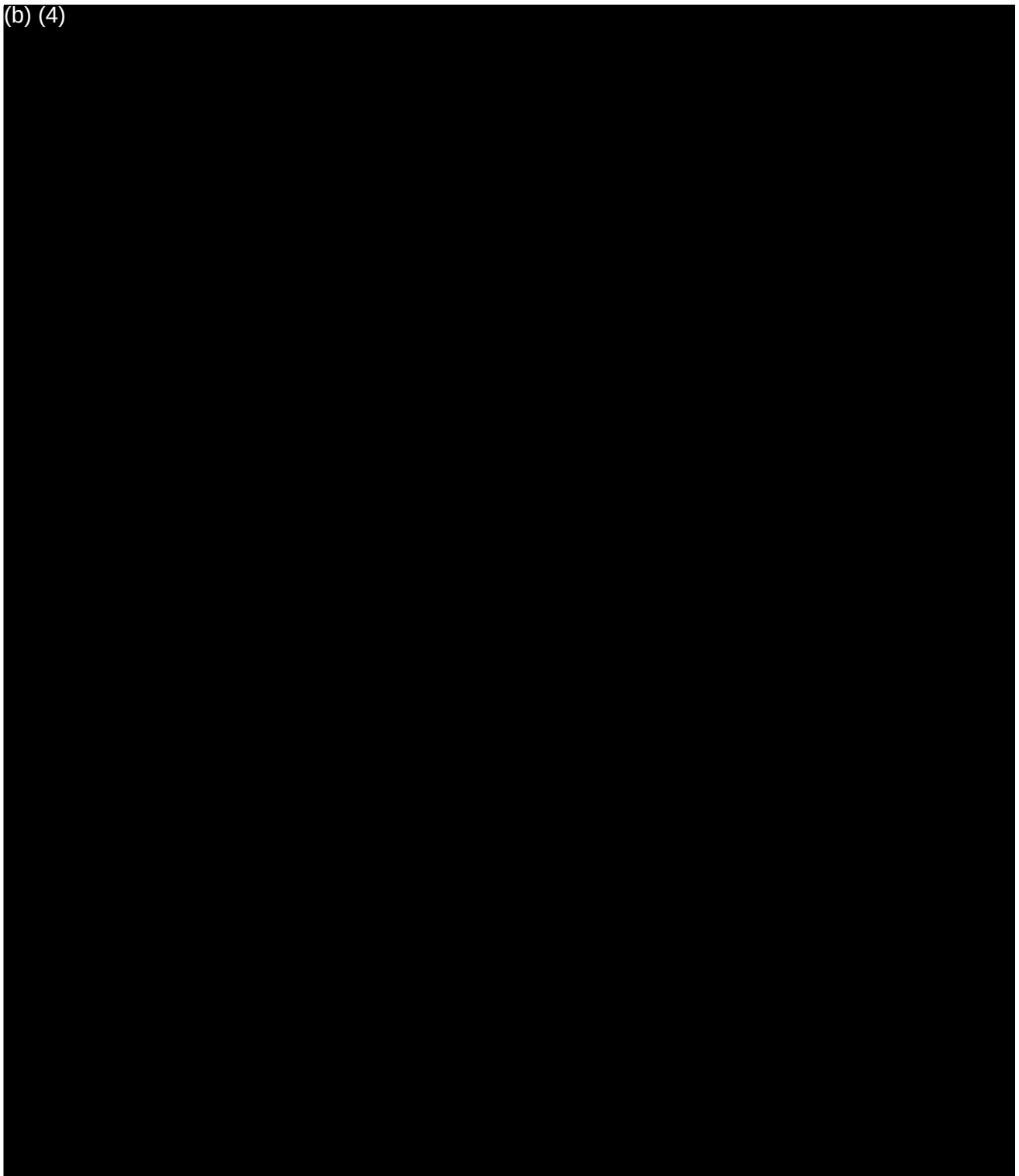
The submission stated that this section is not applicable. It appears that the device does not use software.

X.Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

(b) (4)

[redacted]

(b) (4)



In summary, during normal clinical use as labeled in the Instructions for Use (b) (4)
(b) (4) the possibility of a risk to the patient is exceptionally remote and would necessitate that the clinician to use the device in

(b) (4)

(b) (4) represents an exposure time well outside the directions for use included for the device, and as such, the labeling is adequate and at this time, no further testing is required.

A consult was also obtained from (b) (4) regarding optical safety of the device. In his consult, he determined that in general, the approach outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appeared appropriate. (b) (4)

(b) (4)

Reviewer analysis is that the requests for additional information were fulfilled.

XI.Performance Testing – Bench

The original submission stated that optical power testing and optical wavelength testing were performed (b) (4)

(b) (4)

In S001, the company stated that the report, (b) (4) , addresses the power and wavelength of the LED light sources as a function of time; (b) (4)

(b) (4)

(b) (4)

XII Performance Testing – Animal

The submission does not include any performance testing using animals.

XIII Performance Testing – Clinical

The submission does not include any clinical performance testing.

XIV. Substantial Equivalence Discussion

	Yes	No	
1. Same Indication Statement?	X		If **YES** = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NSE**
3. Same Technological Characteristics?		X	If **YES** = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?		X	If **YES** = Go To 6
5. Descriptive Characteristics Precise Enough?		X	If **NO** = Go To 8 If **YES** = Stop **SE**
6. New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NSE**
7. Accepted Scientific Methods Exist?			If **NO** = Stop **NSE**
8. Performance Data Available?	X		If **NO** = Request Data
9. Data Demonstrate Equivalence?	X		Final Decision: SE

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

3. Describe the new technological characteristics: The submission device differs from the predicate devices in two ways. First, the submission device power source is from primary lithium batteries rather than rechargeable batteries. (b) (4) [redacted]

4. Explain how new characteristics could or could not affect safety or effectiveness: The company provided testing for battery life and provided labeling changes with recommendations for battery replacement based on the performance testing of the battery life and device light output. (b) (4) [redacted]

does the predicate device.

5. Explain how descriptive characteristics are not precise enough: The original submission did not include details of thermal safety, electromagnetic compatibility, and optical safety, as well as did not include clinical data, or adequate labeling.
9. Explain how the performance data demonstrates that the device is or is not substantially equivalent: Additional information including performance testing, clinical data, revisions in the IFUS, and labeling and predicate device comparison provided by the company and reviewed and analyzed by FDA determined that the additional information provided answered FDA's concerns about safety and effectiveness of the device compare to predicate devices, and to FDA's concern about the exposure to oral mucosa to UV light.

XV.Contact History

On October 31st, FDA emailed the sponsor the RTA checklist with comments clarifying the use of the checklist.

On November 2nd, FDA received an email from the company stating that a response to the RTA checklist is forthcoming.

On November 7th, FDA received additional information from the company.

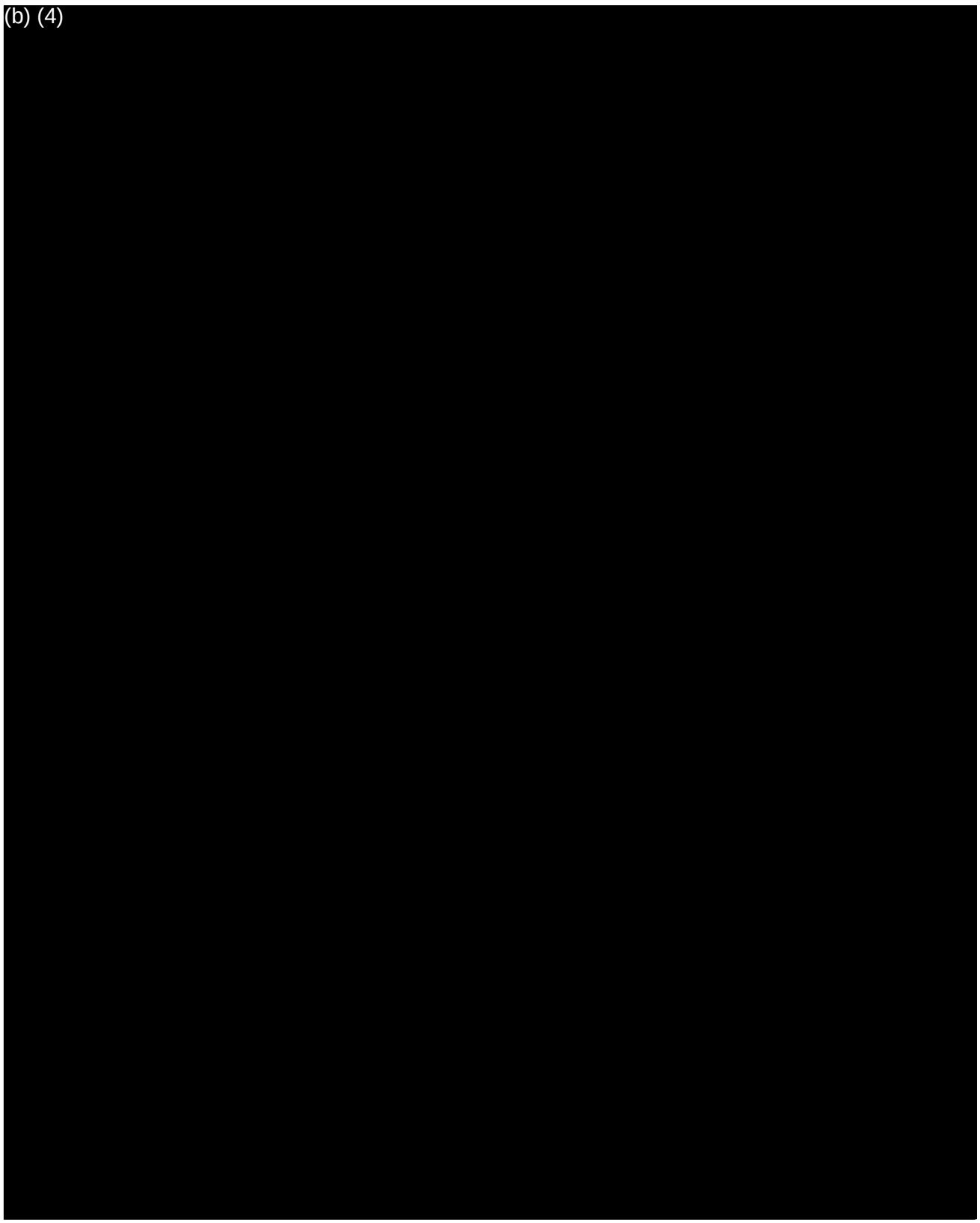
On December 7, 2012, FDA emailed the following request for additional information and the document was placed on telephone hold:

(b) (4)

[redacted]

21

(b) (4)



22

(b) (4)

11. You provided directions for use that include a section on maintenance of your device in which you stated that the device "should be cleaned and disinfected between each patient use."(b) (4)

(b) (4)

12. You referenced ISO 13485 and ISO 14971, however you did not include a risk assessment or the Standards Data Forms for these standards. Please provide a risk assessment for your device, and the Standards Data Forms for all standards referenced.

On December 10th, the company sent an email to FDA confirming receipt of the request for additional information, and requested a teleconference.

On December 11th, FDA emailed the company with a date for the teleconference.

On December 12th, the company sent a confirmation for the teleconference date.

On December 12th, FDA confirmed the DEDB members for the phone call and call in number for the sponsor

On December 13th, the company confirmed the teleconference date again.

On December 15th, a teleconference occurred between FDA (b) (6)

(b) (6) and the company (b) (6)

(b) (4)

exempt(b) (4)

(b) (4)

(b) (4) and that the disinfection and barrier protection recommendations will be addressed in the labeling.

On (b) (4) the company contacted the FDA by email, providing information and a link to the company's draft response.

23

On (b) (4), FDA emailed the company to state that the file sent could not be downloaded, and that the company should send the draft response by email.
On (b) (4), the company emailed the FDA a statement that a CD with the draft response to the telephone hold by FEDEX, and with an email attachment of the first section of the response.
On (b) (4), the FDA confirmed receipt of the CD by FEDEX to the company.
On (b) (4), the sponsor provided the following additional information to FDA, which includes reviewer analysis of the responses:

1. You have provided a device description that includes clinical photographs comparing the use of clinical examination lighting with fluorescent lighting. (b) (4)
(b) (4)
(b) (4) **Reviewer analysis determined that this additional information was acceptable.**
2. You stated in your device description that the batteries power (b) (4)
(b) (4)
(b) (4) **The response was acceptable.**
   b. Please indicate based on bench testing, whether a change in the discharge power of the batteries alters the LED wavelength or light intensity. (b) (4)
(b) (4)
(b) (4) **The response was acceptable.**
   c. Please provide a recommendation of expected battery replacement as indicated by bench performance testing. (b) (4)
(b) (4)
(b) (4) **The response was adequate.**
   d. Please include the recommendation of expected battery replacement in your labeling. (b) (4)
(b) (4)

24

(b) (4) **The response is acceptable.**

3. You stated the length and diameter of your device, and that the material composition for the light is aluminum with grey anodization.
   a. Please provide an engineering drawing to scale of your handpiece device.
   (b) (4)
   (b) (4) **The response was acceptable.**
   b. (b) (4)
   (b) (4) **The response was adequate.**
4. You have stated that the photosensitive glasses are included in this submission, and you stated that the glasses have (b) (4)
   a. (b) (4)
   (b) (4) **. The response was adequate.**
   b. (b) (4)
   (b) (4) **The response was adequate.**
   c. Please provide bench testing to validate the filtering specification for the glasses.
   (b) (4)
   (b) (4) **. The response was adequate.**
5. (b) (4)

25

(b) (4)

maximum temperature (b) (4)
(b) (4)
be sufficient to avoid damage. Thus, the use of the more conservative (b) (4)
(b) (4)

b. Please define "collateral standards EMC/EMI" and provide performance testing for these standards.

(b) (4)

(b) (4) **The response was adequate.**

c. Please provide bench testing to validate maximum recommended time for use of the device and recommended time to allow device to cool before additional use.

(b) (4)

(b) (4) **The response was adequate and supports the duty cycle in the labeling.**

d. Please provide revised labeling to inform the end user of recommended on/off times for use of the device based on the bench testing. **See 5c**

e. Please provide Standards Data Forms for any and all standard to which your testing conforms. The sponsor provided SDRs for IEC 60601-1-2, and IEC 62471. **The response was adequate.**

6. (b) (4)

(b) (4) **. The response was adequate.**

26

7. You referred to electromagnetic compatibility emission testing but you have not referred to immunity testing. Please provide testing to show conformity to immunity or alternatively, please provide a justification for why you have not provided immunity testing. *The company stated that the Electromagnetic Compatibility and Electromagnetic Interference, and the company included the full report with a certificate of compliance.* **The response was adequate.**
8. You have provided in your device description a range of wavelength for your device of (b) (4) (b) (4) [redacted]
9. You provided an Indications for Use Statement that includes a description of your device. The Indications for Use Statement is a statement to simply state indications for use of a device.
    a. Please provide revised Indications for Use Statement. We recommend that you remove the following statements from your Indications for Use Statement:
        "Oral ID™ excites the tissue with blue light and allows for direct visualization of the resulting natural tissue fluorescence. Oral ID™ eyewear is reusable filtered eyewear that is worn by the healthcare professional during the oral examination to enhance the effects of the fluorescence visualization of tissue by the Oral ID blue light. "

    The company provided a revised IFUS. **The response was acceptable.**
    b. Please provide a revised 510(k) Summary and revised labeling with the revised Indications for Use Statement. *The sponsor provided revised DFU and 510(k) Summary with the identical statement to the revised IFUS.* **The response is adequate.**
10. You have provided a 510(k) Summary. FDA conducts a comprehensive review of the 510(k Summary in accordance with 21 CFR 807.92. Based on our assessment of your 510(k) Summary in section 6 of the submission, FDA believes that your Summary does not meet the regulation. Please edit the 510(k) summary as follows:
    a. (b) (4) [redacted]
    b. (b) (4) [redacted]

27

c. (b) (4)

d. (b) (4)

e. (b) (4)

The company provided a revised 510(k) Summary with requested revisions. **The response was adequate.**

11. You provided directions for use that include a section on maintenance of your device in which you stated that the device "should be cleaned and disinfected between each patient use." The external surfaces of the handpiece should be wiped down..." (b) (4)
(b) (4)

The response was adequate.

12. (b) (4)
(b) (4) **. The response was adequate.**

On February 22, the FDA sent the following requests for additional information to the sponsor following review of the responses provided to FDA on February 8th:

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate. (b) (4)
(b) (4)
2. In the thermal safety analysis (b) (4) section 4.1.3, you have indicated that the
(b) (4)
3. (b) (4) , you addressed thermal safety and the enclosed testing report, Appendix J. You have provided data in the thermal safety analysis (b) (4)
(b) (4)
4. (b) (4)

28

(b) (4)

5. (b) (4)

6. (b) (4)

7. (b) (4)

8. You have provided information on the LED source in terms of spectral distribution and intensity, (b) (4)
(b) (4)

9. (b) (4)

In addition, we will speak about the Indications for Use Statement for your device on Monday.

On February 22, the company sent an email to FDA requesting a teleconference for Monday February 25th, and stated that they had a question about the question #5.

On February 26th, the company and FDA held a teleconference about the IFUS and question #5. (b) (4)
(b) (4). The FDA also clarified questions that the sponsor had for question #5.

On February 27th, the company sent FDA response to requests for additional information by email with attachments for responses and test reports, as well as a revised IFUS and revised DFU. On February 27th, FDA confirmed receipt of the response by email to the company. The requests and reviewer analysis are as follows:

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate. (b) (4)
(b) (4)

(b) (4)

(b) (4) **The response was adequate.**

2. (b) (4)

(b) (4)

(b) (4) **The response was adequate.**

3. In response item L, you addressed thermal safety and the enclosed testing report, (b) (4) You have provided data in the thermal safety analysis indicating that the maximum temperature rise produced by this device is approximately (b) (4)

(b) (4)

(b) (4) **The response was adequate.**

30

4 (b) (4) [redacted]

5. You have provided a general, qualitative comparison of the subject and predicate devices. Please provide a quantitative comparison of the light sources -(b) (4) [redacted]

(b) (4) [redacted]

The response was adequate.

6 (b) (4) [redacted]

(b) (4)

(b) (4) **The response was adequate.**

7. (b) (4)

(b) (4) **The response was adequate.**

8. You have provided information on the LED source in terms of spectral distribution and intensity, but not on the spatial profile of illumination, (b) (4)

(b) (4)

(b) (4) **The response was adequate.**

9. (b) (4)

(b) (4) **The response was adequate.**

On March 5th, FDA sent the following request for additional information to the company:

1. (b) (4)

   A. (b) (4)

   B. (b) (4)

2. (b) (4)

32

You may wish to refer to the following link as you revise the 510(k) Summary:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142651.htm#link_7
On March 7th, the company sent an email to FDA with attachments of the revised IFUS (again), a revised 510(k) Summary and a report on radiant energy thermal testing. **The additional information was reviewed (see comment Thermal Safety section) and the response was adequate.**

XVI.Recommendation

Substantially equivalent
Regulation Name: ultraviolet detector
Regulation Number: 21CFR872.6350
Product Code : NXV

Digital Signature Concurrence Table	
Reviewer Sign-Off	Leah S. Royce -S 2013.03.13 08:24:06 -04'00'
Branch Chief Sign-Off	Mary S. Runner -S 2013.03.13 10:58:54 -04'00'
Division Sign-Off	Kwame O. Ulmer -S 2013.03.13 14:47:04 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Consult Memo

Date: 21 January 2013

From: Josh Pfefer, CDRH/OSEL/DP

To: Leah Royce, CDRH/ODE/DAGID/DEDB

CC:

Re: Document #: K123169
Device: OralID
Sponsor: Forward Science LLC

Background and Scope of Review

This consult is comprised of an optics review of the sponsor's 510(k) submission as well as their response to prior deficiencies. Issues include evaluation of optical and thermal safety, comparison of device characteristics and performance to predicate device, as well as the clinical effectiveness of the technique.

Principles of Operation

The subject device includes a light source and eyewear for the clinician to enhance visualization of neoplastic oral mucosa. (b) (4)
(b) (4)
(b) (4) While the intensity of emitted fluorescence from healthy tissue is much lower than that of reflected illumination light, the eyewear reduces visual interference from blue light, enabling the user to visualize the fluorescence. While the mechanisms of changes in endogenous fluorescence are not always clear or consistent, reductions in the normal fluorescence intensity of mucosa can occur due to increased blood content due to angiogenesis, or possibly changes in cellular metabolism or collagen crosslinking. Theoretically, by improving the clinician's ability to visually identify regions with reduced fluorescence intensity, it should be possible to detect and localize changes in fluorescence intensity that are indicative of mucosal neoplasia.

Deficiencies

Optical Safety

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate. (b) (4)
(b) (4)

34

(b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

4. (b) (4)

Other issues

5. You have provided a general, qualitative comparison of the subject and predicate devices. Please provide a quantitative comparison of the light sources – (b) (4)

(b) (4)

6. (b) (4)

7. (b) (4)

8. (b) (4)

35

(b) (4)

9. (b) (4)

Summary

(b) (4)

(b) (6)

Royce, Leah

From: bpikkula@oralid.com
Sent: Thursday, March 07, 2013 2:39 PM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Hi Dr. Royce,

(b) (4)

(b) (4)

Sincerely,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: RE: K123169
From: <bpikkula@oralid.com>
Date: Thu, March 07, 2013 12:23 am
To: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Cc: "Robert Whitman" <RWhitman@oralid.com>

Good Morning Dr. Royce,

Per your request below, attached are the following documents:

(b) (4)

If you have any questions, please feel free to contact me.

Sincerely,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Tue, March 05, 2013 7:45 pm
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Hello Brian:

(b) (4)

Please provide this information by email by Friday March 8th in order for FDA to complete the review of your device. Please feel free to contact me with any questions that you may have.

Sincerely,

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460

37

Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

Royce, Leah

From: Royce, Leah
Sent: Friday, March 08, 2013 7:14 AM
To: 'bpikkula@oralid.com'
Subject: RE: K123169

Good morning Brian:

Thanks for all of the additional information. We are in the process of completing our review. Have a good weekend.

Sincerely,

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Thursday, March 07, 2013 2:39 PM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Hi Dr. Royce,

(b) (4) [redacted]

(b) (4) [redacted]

Sincerely,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

> -------- Original Message --------
> Subject: RE: K123169
> From: <bpikkula@oralid.com>
> Date: Thu, March 07, 2013 12:23 am
> To: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
> Cc: "Robert Whitman" <RWhitman@oralid.com>
>
> Good Morning Dr. Royce,
>
> Per your request below, attached are the following documents:
>
> (b) (4) [redacted]
>
> If you have any questions, please feel free to contact me.
>
> Sincerely,
> Brian
>
> Brian M Pikkula, PhD
> President & CTO
> Forward Science LLC
> 832-526-0150
>
> > -------- Original Message --------
> > Subject: K123169
> > From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
> > Date: Tue, March 05, 2013 7:45 pm
> > To: "bpikkula@oralid.com" <bpikkula@oralid.com>

39

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

V. 510(k) SUMMARY

Submitted by: Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

Contact Person: Brian Pikkula, PhD

Date Prepared: October 04, 2012

Proprietary Name: OralID™

Common Name: Oral Examination Light and Accessories

Classification:

Class II:	21 CFR § 872.6350
Class I: (Exempt)	21 CFR § 886.5850

Classification Name: Ultra-violet Detector – NXV (EAQ)
Photosensitive glasses – HQY (Exempt)

Predicate Devices: DentLight Oral Exan Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

Device Description:

OralID™ is a battery operated (CR123A), hand-held, oral illumination and examination light designed for use by dental and medical professionals to be used as an adjunctive tool for fluorescence visualization of oral mucosal tissue. OralID™ accessories include two pair of filtered eyewear for both the clinician and patient.

Intended Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Technological Characteristics:

OralID™ uses "CR123A" batteries to operate one high intensity LED to emit a visible blue light to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer. While using the filtered glasses and OralID™ oral examination light, healthy tissue fluoresces while abnormal tissue appears dark due to lack of fluorescence.

Substantial Equivalence

OralID™ has the same intended use and technical characteristics as the predicate devices (K101140 and K102083); each uses fluorescence as the primary mode to aid in visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces a violet light and views fluorescence through filtered loupes.

Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens.

OralID™ uses "CR123A" batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk of the recharging process.

The operational principles of the proposed and predicate devices are identical with the primary mode to aid in visualization of tissue through fluorescence. Each of these devices is powered by batteries and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

Performance Testing and Compliance

The following tests were conducted to evaluate the functionality and performance of the proposed OralID™ oral examination light:

- Optical Safety
- Thermal Safety
- Optical Wavelength
- Optical Power Testing
- Beam Quality

OralID™ conforms to electrical safety requirements and complies with the electromagnetic compatibility standards established by IEC 60601-1-2.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): K123169

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

Prescription Use____X____ AND/OR Over-the-Counter_____
(Per 21 CFR 801 Subpart D) (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(b) (4) Radiant Energy Thermal Testing

(b) (4) Radiant Energy Thermal Testing

Hello Brian:

(b) (4)

[redacted]

Sincerely,

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

45

(b) (4) Radiant Energy Thermal Testing

(b) (4) Radiant Energy Thermal Testing

Royce, Leah

From: bpikkula@oralid.com
Sent: Wednesday, February 27, 2013 11:37 AM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Thanks for the note, Dr. Royce.

Brian

-------- Original Message --------
Subject: RE: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Wed, February 27, 2013 10:28 am
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

received. I will be in touch regarding any need to revise the 510(k) Summary.

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Wednesday, February 27, 2013 11:27 AM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Good morning, Dr. Royce.

Attached are several documents.

(b) (4) [redacted]

- (b) (4) [redacted]
-

48

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)
-

I will call shortly to confirm receipt of this email. If you have any questions, please feel free to reach out.

All the Best,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Fri, February 22, 2013 9:30 am
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Good morning Brian:

(b) (4)

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate.

(b) (4)

2. (b) (4)

3. (b) (4)

49

(b) (4)

4. (b) (4)

5. You have provided a general, qualitative comparison of the subject and predicate devices. (b) (4)

(b) (4)

6. (b) (4)

7. (b) (4)

8. (b) (4)

9. (b) (4)

(b) (4)

Sincerely,

Leah

Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002

50

301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

OralID™
A Forward Science Company

INSTRUCTIONS FOR USE

DEVICE DESCRIPTION

OralID™ is a battery operated, hand-held oral examination light to be used as an adjunctive device for oral mucosal screening. Accessories include filtered eyewear for both the clinician and patient.

OralID™ emits a visible blue light into the oral cavity. The OralID™ eyewear is worn by the healthcare professional to enhance the visual effects of the blue light during the examination. Normal, healthy tissue fluoresces green while abnormal tissue appears dark due to lack of fluorescence.

FLUORESENCE TECHNOLOGY

Traditional oral examinations include tactile and visual methods, utilizing reflected light to visualize the oral cavity. OralID™ utilizes fluorescence technology to examine the oral cavity, being able to identify tissue changes in some cases before they become visible to the naked eye.

INTENDED USE

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

⚠ Do not charge batteries (when drained please dispose of them per your local laws or regulations).

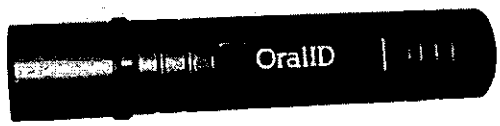
⚠ Do not mix old and new batteries (use batteries in pairs).

⚠ Do not mix different brand batteries.

⚠ Only use high quality, US Manufactured CR123A Energizer batteries.

PACKAGE CONTENTS

- OralID™ Device
- Clinician Filtered Eyewear
- Patient Filtered Eyewear
- 6 CR123A lithium batteries
- IFU (Instructions for use)
- Storage/Display Box



DEVICE REGISTRATION

Please register your OralID™ device online at www.OralID.com/register . Registration will expedite the warranty process of the device and to help keep you informed of the most recent news regarding oral screening.

WARRANTY

Forward Science LLC warrants this equipment to the original purchaser against any manufacturing defects for a period of one (1) year from the original date of purchase. Warranty registration of your OralID™ device at www.OralID.com/register will expedite the warranty process.

The warranty is void if product is not used and maintained according to the Instructions For Use provided with the device.

Should service repair be required, please contact OralID™ Customer Support to obtain instructions and return material authorization (RMA) number. The original purchaser is responsible for shipping and handling charges when returning product for servicing

⚠ Due to the high power LED, this device may be warm to the touch after several minutes of illumination.

⚠ Do not look directly into the light.

52

INITIAL SET UP

The device is shipped ready to use. For battery replacement, insert batteries with the "+" end facing the front of the device, as seen in the picture below.

THE ORALID EXAMINATION

Before any oral examination occurs, please review all of the patient's medical and dental history

1. Conduct a thorough visual and manual oral examination, both extra-oral and intra-oral per the ADA guidelines.
2. The filtered eyewear should be placed on at this time for both the clinician and patient. Both glasses are the same, so the clinician shall choose which glasses fit best.
3. If possible, dim the lights in the operatory (not necessary for use).
4. Press the ON/OFF power button at the back of the device.
5. Using the OralID™ device, repeat the intra-oral examination
   - •Normal tissue emits a green fluorescence
   - •Abnormal tissue appears dark due to lack of fluorescence

   Note: Inflammation typically appears dark due to increased blood vessels.
6. Document all relevant findings. (Documentation forms can be found at www.OralID.com)
7. Inform the patient of any/all relevant findings and appropriate course of action.
8. Follow up in 2 weeks or refer as appropriate.

CONTACT INFORMATION
Phone: 855.MY ORALID (855.696.7254)
Fax: 855.FAX ORALID (855.329.6725)
Web: www.OralID.com
Email: info@OralID.com

MAINTENENCE

OralID™ device should be stored in a cool, dry place. OralID™ shall be cleaned and disinfected between each patient use. The external surfaces of the Handpiece shall then be wiped down with a hospital-grade surface disinfectant and a towelette or gauze, e.g. Caviwipes™ or equivalent. Do not use disinfectants with alcohol content over 70%.

The CDC recommends the use of a sheath during standard procedures as best practice. For a list of approved sheaths, please contact us.

OralID™ is recommended to be turned off for a total of 2 min after each 2 min examination. This will also allow the device to cool prior to the next examination.

OralID ™ batteries shall be replaced after approximately 50 - 2 min. examinations. After the batteries have been utilized for approximately 100 minutes, the light intensity begins to decrease.

Filtered Eyewear (Clinician and Patient)

Filtered eyewear should be cleaned with soap and water. Do not use alcohol or alcohol-based products, as this will degrade the lenses.

CONTRAINDICATIONS

Prior to use of OralID™, healthcare provider should always perform a conventional oral mucosal examination per the ADA guide lines.
There are no known contraindications.

DEVICE SPECIFICATIONS & CARE

- Dimensions 2.4 cm diameter x 12.5 cm length
- Battery: 2 x CR1234A primary lithium
- Battery Life: For a 2 min. exam, batteries should last approximately 50 exams

MANUFACTURER INFORMATION

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479

U.S. Federal law restricts this device to sale by or on the order of a Dentist, Physician, or other appropriately licensed health-care professional.

OralID™ Patent Pending

Remember: The Gold Standard for diagnosing abnormal lesions is a surgical biopsy.

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

February 27, 2013

RE: K123169 – Response to 22-Feb-13 Email Questions

Dear Dr. Royce,

On the following pages and attachments are answers to the questions you submitted via email on February 22, 2013 for the OralID 510(k) application (K123169).

If you have any questions, please contact me by phone at 832-526-0150 or by email at bpikkula@OralID.com.

Sincerely,

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Cell: 832-526-0150
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate. (b) (4)

(b) (4)

(b) (4)

(b) (4)

2. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

3. (b) (4)
(b) (4)

(b) (4)

(b) (4)

4. (b) (4)
(b) (4)

(b) (4)

(b) (4)

S6

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

5. You have provided a general, qualitative comparison of the subject and predicate devices.

(b) (4)

(b) (4)

We do not have access to the predicate devices and thus cannot provide the detailed information requested. (b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

6. (b) (4)
(b) (4)

(b) (4)

(b) (4)

7. (b) (4)
(b) (4)

(b) (4)

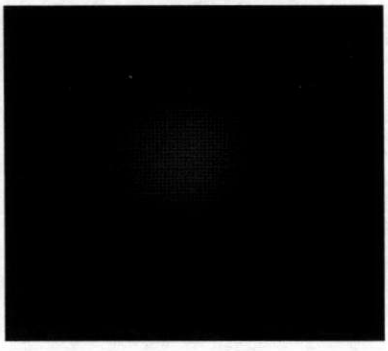
(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

8. (b) (4)

(b) (4)



(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

9. (b) (4)
(b) (4)

(b) (4)

(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

(b) (4) Description of Optical Measurement Test Fixture

(b) (4) Description of Optical Measurement Test Fixture

(b) (4) Description of Optical Measurement Test Fixture

(b) (4) Optical Testing Protocol

(b) (4) Optical Testing Protocol

OralID™
A Forward Science Company

INSTRUCTIONS FOR USE

DEVICE DESCRIPTION

OralID™ is a battery operated, hand-held oral examination light to be used as an adjunctive device for oral mucosal screening. Accessories include filtered eyewear for both the clinician and patient.

OralID™ emits a visible blue light into the oral cavity. The OralID™ eyewear is worn by the healthcare professional to enhance the visual effects of the blue light during the examination. Normal, healthy tissue fluoresces green while abnormal tissue appears dark due to lack of fluorescence.

FLUORESENCE TECHNOLOGY

Traditional oral examinations include tactile and visual methods, utilizing reflected light to visualize the oral cavity. OralID™ utilizes fluorescence technology to examine the oral cavity, being able to identify tissue changes in some cases before they become visible to the naked eye.

INTENDED USE

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

⚠ Do not charge batteries (when drained please dispose of them per your local laws or regulations).

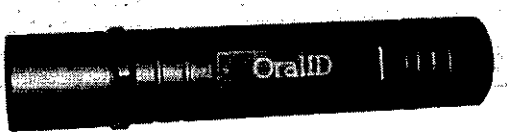
⚠ Do not mix old and new batteries (use batteries in pairs).

⚠ Do not mix different brand batteries.

⚠ Only use high quality, US Manufactured CR123A Energizer batteries.

PACKAGE CONTENTS

- OralID™ Device
- Clinician Filtered Eyewear
- Patient Filtered Eyewear
- 6 CR123A lithium batteries
- IFU (Instructions for use)
- Storage/Display Box



DEVICE REGISTRATION

Please register your OralID™ device online at www.OralID.com/register . Registration will expedite the warranty process of the device and to help keep you informed of the most recent news regarding oral screening.

WARRANTY

Forward Science LLC warrants this equipment to the original purchaser against any manufacturing defects for a period of one (1) year from the original date of purchase. Warranty registration of your OralID™ device at www.OralID.com/register will expedite the warranty process.

The warranty is void if product is not used and maintained according to the Instructions For Use provided with the device.

Should service repair be required, please contact OralID™ Customer Support to obtain instructions and return material authorization (RMA) number. The original purchaser is responsible for shipping and handling charges when returning product for servicing

⚠ Due to the high power LED, this device may be warm to the touch after several minutes of illumination.

⚠ Do not look directly into the light.

INITIAL SET UP

The device is shipped ready to use. For battery replacement, insert batteries with the "+" end facing the front of the device, as seen in the picture below.

THE ORALID EXAMINATION

Before any oral examination occurs, please review all of the patient's medical and dental history.

1. Conduct a thorough visual and manual oral examination, both extra-oral and intra-oral per the ADA guidelines.
2. The filtered eyewear should be placed on at this time for both the clinician and patient. Both glasses are the same, so the clinician shall choose which glasses fit best.
3. If possible, dim the lights in the operatory (not necessary for use).
4. Press the ON/OFF power button at the back of the device.
5. Using the OralID™ device, repeat the intra-oral examination
   - •Normal tissue emits a green fluorescence
   - •Abnormal tissue appears dark due to lack of fluorescence

   Note: Inflammation typically appears dark due to increased blood vessels.
6. Document all relevant findings. (Documentation forms can be found at www.OralID.com)
7. Inform the patient of any/all relevant findings and appropriate course of action.
8. Follow up in 2 weeks or refer as appropriate.

CONTACT INFORMATION
Phone: 855.MY ORALID (855.696.7254)
Fax: 855.FAX ORALID (855.329.6725)
Web: www.OralID.com
Email: info@OralID.com

MAINTENENCE

OralID™ device should be stored in a cool, dry place. OralID™ shall be cleaned and disinfected between each patient use. The external surfaces of the Handpiece shall then be wiped down with a hospital-grade surface disinfectant and a towelette or gauze, e.g. Caviwipes™ or equivalent. Do not use disinfectants with alcohol content over 70%.

The CDC recommends the use of a sheath during standard procedures as best practice. For a list of approved sheaths, please contact us.

OralID™ is recommended to be turned off for a total of 2 min after each 2 min examination. This will also allow the device to cool prior to the next examination.

OralID ™ batteries shall be replaced after approximately 50 - 2 min. examinations. After the batteries have been utilized for approximately 100 minutes, the light intensity begins to decrease.

Filtered Eyewear (Clinician and Patient)

Filtered eyewear should be cleaned with soap and water. Do not use alcohol or alcohol-based products, as this will degrade the lenses.

CONTRAINDICATIONS

Prior to use of OralID™, healthcare provider should always perform a conventional oral mucosal examination per the ADA guide lines.
There are no known contraindications.

DEVICE SPECIFICATIONS & CARE

- Dimensions 2.4 cm diameter x 12.5 cm length
- Battery: 2 x CR1234A primary lithium
- Battery Life: For a 2 min. exam, batteries should last approximately 50 exams

MANUFACTURER INFORMATION

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479

U.S. Federal law restricts this device to sale by or on the order of a Dentist, Physician, or other appropriately licensed health-care professional.

OralID™ Patent Pending

Remember: The Gold Standard for diagnosing abnormal lesions is a surgical biopsy.

REF FS-10 v1.2

67

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): K123169

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by a dentist or physician as an adjunct to an oral examination to aid in visualization of oral mucosal abnormalities, such as oral cancer and pre-cancer.

Prescription Use____X____ AND/OR Over-the-Counter_____
(Per 21 CFR 801 Subpart D) (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

February 27, 2013

RE: K123169 – Response to 22-Feb-13 Email Questions

Dear Dr. Royce,

On the following pages and attachments are answers to the questions you submitted via email on February 22, 2013 for the OralID 510(k) application (K123169).

If you have any questions, please contact me by phone at 832-526-0150 or by email at bpikkula@OralID.com.

Sincerely,

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Cell: 832-526-0150
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

1. In general, the approach you have outlined for optical safety evaluation based on the IEC 62471 standard for lamp sources appears appropriate. (b) (4)

(b) (4)

(b) (4)

(b) (4)

2. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

3. (b) (4)
(b) (4)

(b) (4)

(b) (4)

4. (b) (4)
(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

5. (b) (4)
(b) (4)

(b) (4)

We do not have access to the predicate devices and thus cannot provide the detailed information requested. (b) (4)
(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

6. (b) (4)
(b) (4)

(b) (4)

(b) (4)

7. (b) (4)
(b) (4)

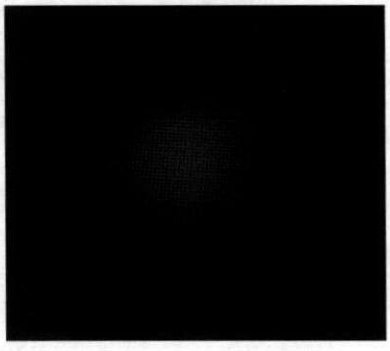
(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

8. (b) (4)
(b) (4)



(b) (4)

(b) (4)

(b) (4)

74

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

9. (b) (4)
(b) (4)

(b) (4)

(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

(b) (4) Test Protocol

(b) (4) Test Protocol

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

February 19, 2013

RE: K123169 – Response to Request for Additional Clinical Images

Dear Dr. Royce:

On the following pages are clinical images of Patients C and D which are provided in response to the request for additional imaging from the OralID 510(k) application (K123169).

If you have any questions, please contact me by phone at 832-526-0150 or by email at bpikkula@OralID.com.

Sincerely,

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Cell: 832-526-0150
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

Patient History:

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

Patient History:

(b) (4)

(b) (4)

(b) (4)

Royce, Leah

From: bpikkula@oralid.com
Sent: Tuesday, February 05, 2013 1:48 PM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Thanks very much for the note, Dr. Royce. We look forward to your thoughts on the sufficiency of the response.
Sincerely,
Brian

-------- Original Message --------
Subject: RE: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Tue, February 05, 2013 10:53 am
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Received the FedEx package just now. Wanted to let you know.

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Monday, February 04, 2013 11:49 PM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Hi Dr. Royce,

Thanks for getting back to me. Not being able to retrieve documents from an external site was a concern of ours.

We have sent via FedEx (tracking # 794674225217) a CD of the draft response to the telephone hold. It is scheduled to arrive no later than 10:30am on Tuesday. However, I am not sure if it will make it to your office before the time on Wednesday you have allotted to review our draft response. So to cover all bases, I have attached the first section of the response which provides answers to the questions of the telephone hold.

If you have any questions or need anything further, please feel free to contact me at your convenience.

Sincerely,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: RE: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Mon, February 04, 2013 4:03 pm
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Hi Brian:

Thank you for your telephone inquiry. While your file is large, I can not download the file (b) (4) (b) (4) here at FDA. Can you determine whether you can provide it as an attachment to an email, and if so, send it to me at your earliest convenience? Otherwise, you may choose to submit your official response to the Document Control Center (DCC) with a hard copy and an eCopy. Once your response has cleared the DCC, I will receive the file and I can begin the formal review.

Please let me know if you have additional questions.

Sincerely,

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Friday, January 25, 2013 2:48 AM
To: Royce, Leah
Cc: Robert Whitman
Subject: RE: K123169

Hi Dr. Royce,

(b) (4)

82

(b) (4) [redacted]

As the file is large (~50Mb), (b) (4) [redacted]
(b) (4) [redacted]

(b) (4) [redacted]

If you have any questions or need clarification, please feel free to reach out. We look forward to your reply.

Have a great weekend,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: RE: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Fri, December 21, 2012 9:54 am
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Received and thank you! Happy holidays! Peace in the New Year

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Thursday, December 20, 2012 11:15 PM
To: Royce, Leah; Runner, Susan
Subject: RE: K123169

Drs. Royce & Runner,

83

I wanted to follow up and thank you both for your time last week. It was a very constructive call which I believe will reduce the number of iterations for this 510(k). Below are the take-aways from the three items we discussed which Forward Science had specific questions about.

(b) (4) Photosensitive Glasses

(b) (4)

(b) (4) Performance Testing

(b) (4)

(b) (4) Sterilization Process / Sheath

(b) (4)

(b) (4)

(b) (4)

If we do not communicate beforehand, Happy Holidays and have a great New Year!

Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: RE: K123169
From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
Date: Wed, December 12, 2012 4:43 pm
To: "bpikkula@oralid.com" <bpikkula@oralid.com>

Hello Brian:

Dr. Susan Runner, branch chief dental devices, and myself will be on the call. You can call us at (b) (4) at 9:00 am.

84

Sincerely,
Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Wednesday, December 12, 2012 8:59 AM
To: Royce, Leah
Subject: RE: K123169

Good Morning Dr. Royce,

9am (EST) will work on Friday. Please provide the best number to reach you.

I may have my colleague, Robert Whitman, on the call. Will others from your team will be joining you?

I look forward to speaking with you.

Sincerely,
Brian

> -------- Original Message --------
> Subject: RE: K123169
> From: "Royce, Leah" <Leah.Royce@fda.hhs.gov>
> Date: Tue, December 11, 2012 8:56 pm
> To: "bpikkula@oralid.com" <bpikkula@oralid.com>
>
> Hello Brian:
>
> Friday is the better day, and the times that I can offer are early in the morning, ie. 9:00, 9:30 or 10:00. The afternoon may work for us too, but we are not available until 1:30. Hope one of these times works for you.
>
> Sincerely,
>
> *Leah*
> *Leah S. Royce, D.D.S.*
> *Dental Devices Branch*
> *Center for Devices and Radiological Health*
> *Food and Drug Administration*

85

10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

From: bpikkula@oralid.com [mailto:bpikkula@oralid.com]
Sent: Monday, December 10, 2012 2:44 PM
To: Royce, Leah
Subject: RE: K123169

Good Afternoon Dr. Royce,

(b) (4)

[redacted]

(b) (4)

[redacted]

Sincerely,
Brian

Brian M Pikkula, PhD
President & CTO
Forward Science LLC
832-526-0150

-------- Original Message --------
Subject: K123169
From: "Royce, Leah"
<Leah.Royce@fda.hhs.gov>
Date: Fri, December 07, 2012 3:22 pm
To: "bpikkula@oralid.com"
<bpikkula@oralid.com>
Cc: "Royce, Leah" <Leah.Royce@fda.hhs.gov>

Good afternoon Brian:

86

(b) (4)

1. (b) (4)

2. (b) (4)

3. (b) (4)

(b) (4)

4. (b) (4)

G. (b) (4)

H. (b) (4)

I. (b) (4)

5. (b) (4)

J. (b) (4)

K.

L.

M.

N.

6. (b) (4)

88

(b) (4)

7. (b) (4)

8. (b) (4)

9. (b) (4)

89

(b) (4)

B. (b) (4)

10. (b) (4)

A. (b) (4)

B. (b) (4)

C. (b) (4)

D. (b) (4)

E. (b) (4)

1. (b) (4)

(b) (4)

2. (b) (4)

I am placing this document on telephone hold pending the submission of information in response to these requests, and the determination that the information fulfills each request. In order to remove this document from its hold status, you must submit this information in hard copy to the Document Control Center at the same address to which your original submission was sent. I am available to review any information you are considering before its official submission in order to ensure that it fulfills these requests.

Sincerely,

Leah
Leah S. Royce, D.D.S.
Dental Devices Branch
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
WO66-G460
Silver Spring, MD 20993-0002
301-796-6268
Fax 301-847-8109
leah.royce@fda.hhs.gov

91

K123169/S001

K18

FORWARD SCIENCE LLC

2511 Wind Fall Ln
Sugar Land. TX 77459 USA
855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

February 09, 2013

RE: K123169/S001 – Replacement eCopy - Response to Telephone Hold

Dear Dr. Royce:

Following please find Forward Science's response to the Telephone Hold placed on the OralID 510(k) submission, K123169.

Per the new requirements, in addition to a paper copy, we are submitting an eCopy. **The eCopy is an exact duplicate of the paper copy**.

If you have any questions regarding this response, please contact me by phone at 832-526-0150 or by email at bpikkula@oralID.com.

Sincerely Yours,

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Cell: 832-526-0150
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Food and Drug Administration
CDRH/ODE
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

February 09, 2013

RE: K123169/S001 – Replacement eCopy - Response to Telephone Hold

Dear Dr. Royce:

Following please find Forward Science's response to the Telephone Hold placed on the OralID 510(k) submission, K123169.

Per the new requirements, in addition to a paper copy, we are submitting an eCopy. **The eCopy is an exact duplicate of the paper copy**.

If you have any questions regarding this response, please contact me by phone at 832-526-0150 or by email at bpikkula@oralID.com.

Sincerely Yours,

Brian Pikkula, PhD
President & CTO
Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479
Cell: 832-526-0150
Ph: 855-696-7254
Fax: 855-329-6725

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

1. (b) (4)

(b) (4)

2. (b) (4)

A. (b) (4)

(b) (4)

Technological Characteristics:

(b) (4)

B. (b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

C. (b) (4)

(b) (4)

(b) (4)

D. Please include the recommendation of expected battery replacement in your labeling.

The recommendation of expected battery replacement is updated in the Instructions For Use labeling, Appendix D. It is located in the Maintenance section. The addition is also listed below.

Maintenance

OralID™ batteries shall be replaced after approximately 50 - 2 min. examinations. After the batteries have been utilized for approximately 100 minutes, the light intensity begins to decrease.

3. (b) (4)

E. (b) (4)

(b) (4) .

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

F. (b) (4)

(b) (4)

4. (b) (4)

G. (b) (4)

(b) (4)

H. (b) (4)

(b) (4)

I. (b) (4)

(b) (4)

5. (b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

J. (b) (4)

(b) (4)

(b) (4)

K. Please define "collateral standards EMC/EMI" and provide performance testing for these standards.

EMC/EMI collateral standards are the standards provided in IEC 60601-1-2 regarding to Electromagnetic Compatibility and Electromagnetic Interference.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

The Electromagnetic Compatibility and Electromagnetic Interference Testing report, 14107-10, (b) (4), verifies that the device complies with all electrical safety requirements defined in IEC 60601-1-2.

For further details, refer to Appendix M for the full report for Electromagnetic Compatibility and Electromagnetic Interference Testing, specifically page 5 for the certificate of compliance.

L. (b) (4)

(b) (4)

(b) (4)

(b) (4)

M. Please provide revised labeling to inform the end user of recommended on/off times for use of the device based on the bench testing.

The Instructions For Use labeling has been revised to reflect the recommended on/off times resulting from (b) (4). The Instructions For Use labeling is attached as Appendix D. The recommendation is shown below as well:

Maintenance

OralID™ batteries shall be replaced after approximately 50 - 2 min. examinations. After the batteries have been utilized for approximately 100 minutes, the light intensity begins to decrease.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

N. Please provide Standards Data Forms for any and all standard to which your testing conforms.

Standards Data Forms are attached in Appendix N. The following Standards Data Forms have been submitted:

IEC 60601, IEC 60601-1-2, IEC 62471, ISO 13485, ISO 14971

6. (b) (4) [redacted]

The Electromagnetic Compatibility and Electromagnetic Interference Testing report, 14107-10, (b) (4) [redacted], verifies that the device complies with all electrical safety requirements defined in IEC 60601-1-2.

For further details, refer to Appendix M for the full report for Electromagnetic Compatibility and Electromagnetic Interference Testing, specifically page 5 for the certificate of compliance.

7. You referred to electromagnetic compatibility emission testing but you have not referred to immunity testing. Please provide testing to show conformity to immunity or alternatively, please provide a justification for why you have not provided immunity testing.

The Electromagnetic Compatibility and Electromagnetic Interference Testing report, 14107-10, (b) (4) [redacted], verifies that the device complies with all electrical safety requirements defined in IEC 60601-1-2.

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

For further details, refer to Appendix M for the full report for Electromagnetic Compatibility and Electromagnetic Interference Testing, specifically page 5 for the certificate of compliance.

8. **You have provided in your device description a range of wavelength for your device**

(b) (4)

(b) (4)

(b) (4)

9. **You provided an Indications for Use Statement that includes a description of your device. The Indications for Use Statement is a statement to simply state indications for use of a device.**

A. Please provide revised Indications for Use Statement. We recommend that you remove the following statements from your Indications for Use Statement:

(b) (4)

Revised Indications for Use Statement is attached as Appendix P. The changes are also listed below:

2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Indications For Use:

OralID™ is intended to be used by qualified health-care providers to aid in visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

(b) (4)

B. Please provide a revised 510(k) Summary and revised labeling with the revise Indications for Use Statement.

Revised 510(k) Summary is attached as Appendix B.

Revised Indications for Use Statement is attached as Appendix P

10. You have provided a 510(k) Summary. FDA conducts a comprehensive review of the 510(k) Summary in accordance with 21 CFR 807.92. (b) (4)

(b) (4)

A. (b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

B. (b) (4)

(b) (4)

Technological Characteristics:

(b) (4)

C. (b) (4)

(b) (4)

D. Please remove the words (b) (4) **and " and replace with** (b) (4) (b) (4) **....**

The changes have been made and a revised 510(k) Summary is attached as Appendix B, along with a revised section below:

E. (b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

The section has been removed and a revised 510(k) Summary is attached as Appendix B.

1. (b) (4)

The Instructions For Use labeling has been updated regarding infection control in the maintenance section. The updated labeling can be found attached on Instructions For Use, Appendix D. The updated maintenance section is below as well:

Maintenance

OralID shall be cleaned and disinfected between each patient use. The external surfaces of the Handpiece shall be wiped down with a hospital-grade surface disinfectant and a towelette or gauze, e.g. Caviwipes™ or equivalent. Do not use disinfectants with alcohol content over 70%.

The CDC recommends the use of a sheath during standard procedures as best practice. For a list of approved sheaths please contact us.

(b) (4)

(b) (4)

2. (b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

The Risk Assessment is attached as Appendix R.

Standards Data Forms are attached as Appendix N.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

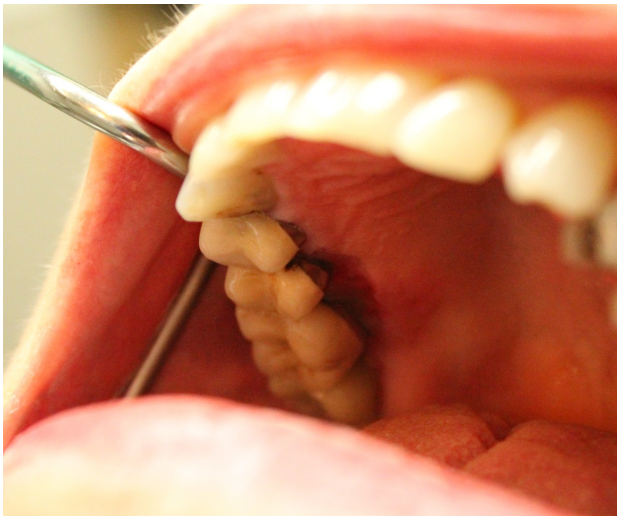
Appendix A – Clinical Images

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Patient A

Patient History:

- 80 Years Old White Female
- Lesion: Upper Right Palate at Gingival Margin #4
- Color: White to Red
- Recall: 10 days, lesion became larger
- Texture: Firm lesion; no fluid when punched with needle



White light image

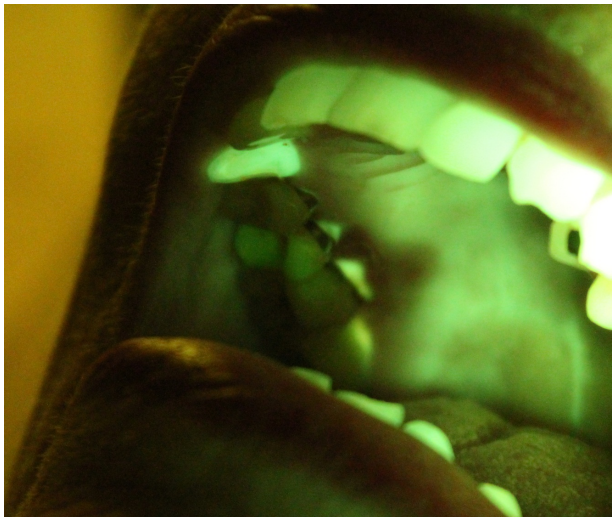


Image using OralID

Pathology Results

- Specimen Size: 1.0cm x 0.5cm x 0.5cm
- Pathology: Moderately Differentiated Invasive Squamous Cell Carcinoma
- Referred to May Clinic

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

(b) (4) Optical Testing Protocol

Patient History:

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix B – 510(k) Summary

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

V. 510(k) SUMMARY

Submitted by: Forward Science LLC
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

Contact Person: Brian Pikkula, PhD

Date Prepared: October 04, 2012

Proprietary Name: OralID™

Common Name: Oral Examination Light and Accessories

Classification:

Class II:	21 CFR § 872.6350
Class I: (Exempt)	21 CFR § 886.5850

Classification Name: Ultra-violet Detector – NXV (EAQ)
Photosensitive glasses – HQY (Exempt)

Predicate Devices: DentLight Oral Exan Light Kit (K101140)
DentLight Inc
1411 E. Campbell Rd, Suite 500
Richardson, TX 75081

VELscope Vx (K102083)
LED Medical Diagnostics
235 – 5589 Byrne Road
Burnaby, BC, Canada, V5J 3J1

Device Description:

OralID™ is a battery operated (CR123A), hand-held, oral illumination and examination light designed for use by dental and medical professionals to be used as an adjunctive tool for fluorescence visualization of oral mucosal tissue. OralID™ accessories include two pair of filtered eyewear for both the clinician and patient.

Intended Use:

OralID™ is intended to be used by qualified health-care providers to aid in visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

(b) (4)

[redacted]

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

Technological Characteristics:

OralID™ uses "CR123A" batteries to operate one high intense LED to emit a visible blue light to aid in visualization of oral mucosal abnormities that may not be apparent or visible to the naked eye. While using the filtered glasses, OralID™ oral examination light shows healthy tissue in fluorescence green while abnormal tissue appears dark due to lack of fluorescence.

Substantial Equivalence

OralID™ has the same intended use and technical characteristics as the predicate devices (K101140 and K102083); each uses fluorescence as the primary mode to aid in visualization of tissue for determining oral tissue abnormalities.

Predicate K101140 uses rechargeable batteries to power high-intensity LEDs that produces a violet light and views fluorescence through filtered loupes.

Predicate K102083 uses rechargeable lithium ion batteries to power high-intensity LEDs that produce blue light and views fluorescence through a hand piece with a filtered lens.

OralID™ uses "CR123A" batteries to power a high-intensity LED that produces blue light as illumination for excitation for tissue fluorescence viewed through filtered eyewear.

The only technological difference from the predicate devices is the power source. While both predicate devices use rechargeable batteries, OralID™ uses primary CR123A batteries to power the device, which decreases the electrical safety risk of the recharging process.

The operational principles of the proposed and predicate devices are identical with the primary mode to aid in visualization of tissue through fluorescence. Each of these devices is powered by batteries and uses LED technology to illuminate the oral cavity view the tissue fluorescence through a filtered lens.

The design, materials, method of operation, and labeling are substantially equivalent.

OralID™ is substantially equivalent to the cleared predicate devices.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix C –
Battery Longevity Test Report

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix D – Instructions for Use

OralID™
A Forward Science Company

INSTRUCTIONS FOR USE

DEVICE DESCRIPTION

OralID™ is a battery operated, hand-held oral examination light to be used as an adjunctive device for oral mucosal screening. Accessories include filtered eyewear for both the clinician and patient.

OralID™ emits a visible blue light into the oral cavity. The OralID™ eyewear is worn by the healthcare professional to enhance the visual effects of the blue light during the examination. Normal, healthy tissue fluoresces green while abnormal tissue appears dark due to lack of fluorescence.

FLUORESENCE TECHNOLOGY

Traditional oral examinations include tactile and visual methods, utilizing reflected light to visualize the oral cavity. OralID™ utilizes fluorescence technology to examine the oral cavity, being able to identify tissue changes in some cases before they become visible to the naked eye.

INTENDED USE

OralID™ is intended to be used by qualified health-care providers to aid in visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

(b) (4)

⚠ Do not charge batteries (when drained please dispose of them per your local laws or regulations).

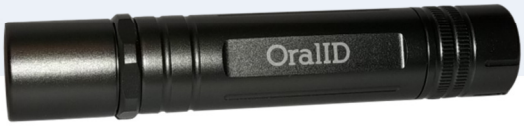
⚠ Do not mix old and new batteries (use batteries in pairs).

⚠ Do not mix different brand batteries.

⚠ Only use high quality, US Manufactured CR123A Energizer batteries.

PACKAGE CONTENTS

- OralID™ Device
- Clinician Filtered Eyewear
- Patient Filtered Eyewear
- 6 CR123A lithium batteries
- IFU (Instructions for use)
- Storage/Display Box



DEVICE REGISTRATION

Please register your OralID™ device online at www.oralid.com/register . Registration will expedite the warranty process of the device and to help keep you informed of the most recent news regarding oral screening.

WARRANTY

Forward Science LLC warrants this equipment to the original purchaser against any manufacturing defects for a period of one (1) year from the original date of purchase. Warranty registration of your OralID™ device at www.oralid.com/register will expedite the warranty process.

The warranty is void if product is not used and maintained according to the Instructions For Use provided with the device.

Should service repair be required, please contact OralID™ Customer Support to obtain instructions and return material authorization (RMA) number. The original purchaser is responsible for shipping and handling charges when returning product for servicing

⚠ Due to the high power LED, this device may be warm to the touch after several minutes of illumination.

⚠ Do not look directly into the light.

INITIAL SET UP

The device is shipped ready to use. For battery replacement, insert batteries with the "+" end facing the front of the device, as seen in the picture below.

THE ORALID EXAMINATION

Before any oral examination occurs, please review all of the patient's medical and dental history

1. Conduct a thorough visual and manual oral examination, both extra-oral and intra-oral per the ADA guidelines.
2. The filtered eyewear should be placed on at this time for both the clinician and patient. Both glasses are the same, so the clinician shall choose which glasses fit best.
3. If possible, dim the lights in the operatory (not necessary for use).
4. Press the ON/OFF power button at the back of the device.
5. Using the OralID™ device, repeat the intra-oral examination
   - •Normal tissue emits a green fluorescence
   - •Abnormal tissue appears dark due to lack of fluorescence

   Note: Inflammation typically appears dark due to increased blood vessels.
6. Document all relevant findings. (Documentation forms can be found at www.oralid.com)
7. Inform the patient of any/all relevant findings and appropriate course of action.
8. Follow up in 2 weeks or refer as appropriate.

CONTACT INFORMATION

Phone: 855.MY ORALID (855.696.7254)
Fax: 855.FAX ORALID (855.329.6725)
Web: www.oralid.com
Email: info@oralid.com

MAINTENENCE

OralID™ device should be stored in a cool, dry place. OralID™ shall be cleaned and disinfected between each patient use. The external surfaces of the Handpiece shall then be wiped down with a hospital-grade surface disinfectant and a towelette or gauze, e.g. Caviwipes™ or equivalent. Do not use disinfectants with alcohol content over 70%.

The CDC recommends the use of a sheath during standard procedures as best practice. For a list of approved sheaths, please contact us.

OralID™ is recommended to be turned off for a total of 2 min after each 2 min examination. This will also allow the device to cool prior to the next examination.

OralID™ batteries shall be replaced after approximately 50 - 2 min. examinations. After the batteries have been utilized for approximately 100 minutes, the light intensity begins to decrease.

Filtered Eyewear (Clinician and Patient)
Filtered eyewear should be cleaned with soap and water. Do not use alcohol or alcohol-based products, as this will degrade the lenses.

CONTRAINDICATIONS

Prior to use of OralID™, healthcare provider should always perform a conventional oral mucosal examination per the ADA guide lines.
There are no known contraindications.

DEVICE SPECIFICATIONS & CARE

- Dimensions 2.4 cm diameter x 12.5 cm length
- Battery: 2 x CR1234A primary lithium
- Battery Life: For a 2 min. exam, batteries should last 50 exams

MANUFACTURER INFORMATION

Forward Science LLC
2511 Wind Fall Ln
Sugar Land, TX 77479

U.S. Federal law restricts this device to sale by or on the order of a Dentist, Physician, or other appropriately licensed health-care professional.

OralID™ Patent Pending

Remember: The Gold Standard for diagnosing abnormal lesions is a surgical biopsy.

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix E –
Scale Drawing of OralID

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

(b) (4)

[redacted]

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix F – Eyewear Spectra

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix G – Life Cycle Testing

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix H – Cleaning & Disinfection and Durability of Markings

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix I – Insertion of Battery Backwards

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix J – Thermal Testing

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix K –
Push & Drop Testing

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix L – Shorting of LED Terminals

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix M – Electromagnetic Compatibility Test Report

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix N – Standards Data Forms

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

IEC 60601 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, 2005

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 5-4	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☑	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

60601 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, 2005

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.2.11	Mode of Operation	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.1.3	Durability of markings	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.2.2	Identification	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

IEC 60601 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, 2005

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.3.3	Batteries	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
15.4.3.4	Lithium batteries	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.3.2	Instructions for use	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

IEC 60601 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, 2005

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
7.9.3.1	Technical description - General	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
10.4	Lasers and light emitting diodes (LEDs)	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

Used IEC 62471 instead of recommended IEC 60825

DESCRIPTION

JUSTIFICATION

IEC 60825 pertains to lasers. The OralID light source is an LED whose applicable safety standard is IEC 62471.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
11.1.1	Maximum temperature during NORMAL USE	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

IEC 60601 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, 2005

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
11.6.6	Cleaning and disinfection of ME EQUIPMENT and ME SYSTEMS	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
15.3.2	Push Test	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
15.3.4.1	Drop test - HAND-HELD ME EQUIPMENT	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

IEC 60601-1-2 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential... 2007

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 5.34	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☑	☐
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

PSC Graphics (301) 443-6740 EF

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

IEC 62471 Photobiological safety of lamps and lamp systems, 2006

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2] ?	☑	☐
FDA Recognition number [3]	# 029	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☑	☐
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5] ?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

PSC Graphics (301) 443-6740 EF

EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE

IEC 62471 Photobiological safety of lamps and lamp systems, 2006

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.3.1	Actinic UV hazard exposure limit for the skin and eye	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.3.3	Retinal blue light hazard exposure limit	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.3.5	Retinal thermal hazard exposure limit	☑ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED ❖

DESCRIPTION

JUSTIFICATION

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

❖ Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

Paperwork Reduction Act Statement

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes, 2003

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☐	☑
FDA Recognition number [3] #		
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☑	☐
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

Form Approved: OMB No. 0910-0120; Expiration Date: 12/31/13

Department of Health and Human Services
Food and Drug Administration

STANDARDS DATA REPORT FOR 510(k)s

(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

TYPE OF 510(K) SUBMISSION

☑ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 14971 Medical devices — Application of risk management to medical devices, 2007

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☑	☐
FDA Recognition number [3]	# 5-70	
Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?	☐	☑
Is a summary report [4] describing the extent of conformance of the standard used included in the 510(k)? If no, complete a summary report table.	☑	☐
Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?	☑	☐
Does this standard include acceptance criteria? If no, include the results of testing in the 510(k).	☐	☑
Does this standard include more than one option or selection of tests? If yes, report options selected in the summary report table.	☐	☑
Were there any deviations or adaptations made in the use of the standard?	☐	☑
If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5]?	☐	☐
Were deviations or adaptations made beyond what is specified in the FDA SIS? If yes, report these deviations or adaptations in the summary report table.	☐	☑
Were there any exclusions from the standard? If yes, report these exclusions in the summary report table.	☐	☑
Is there an FDA guidance [6] that is associated with this standard?	☐	☑
If yes, was the guidance document followed in preparation of this 510k?	☐	☐

Title of guidance: _____

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], www.fda.gov/cdrh/stdsprog.html

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.

[5] The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[6] The online search for CDRH Guidance Documents can be found at www.fda.gov/cdrh/guidance.html

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix O – Evaluation of Optical Safety

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix P – Indications For Use Statement

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77479 USA
Ph: 855-696-7254

IV. Indications for Use

Applicant: **Forward Science LLC**
2511 Wind Fall Lane
Sugar Land, TX 77479
Ph: 855-696-7254
Fax: 855-329-6725

510(k) Number (if Known): K123169

Device Name: **OralID™**

Indications For Use:

OralID™ is intended to be used by qualified health-care providers to aid in visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer and premalignant dysplasia.

(b) (4)

[redacted]

Prescription Use X (Per 21 CFR 801 Subpart D) AND/OR Over-the-Counter ____ (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix Q – Disposable Sleeve Optical Testing

(b) (4)

(b) (4)

FORWARD SCIENCE LLC
2511 Wind Fall Ln
Sugar Land, TX 77459 USA
855-696-7254

Appendix R – Risk Assesment

(b) (4)

(b) (4)

(b) (4)

(b) (4)