U.S. Department of Health & Human Services

Food and Drug Administration

SAVE REQUEST

USER:	(cwf)
FOLDER:	K122337 - 1982 pages
COMPANY:	FERTILITY FOCUS LTD (FERTFOCU)
PRODUCT:	DEVICE, FERTILITY DIAGNOSTIC, PROCEPTIVE (LHD)
SUMMARY:	Product: OVUSENSE
DATE REQUESTED:	Apr 9, 2015
DATE PRINTED:	Apr 9, 2015
Note:	Printed

510(k) Summary

fertility focus

This 510(k) summary of safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

DATE:	July 30, 2013
APPLICANT:	Fertility Focus Ltd. Robert Milnes, CEO Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW Tel: 044-1494-510272 Email: robert.milnes@fertility-focus.com
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION:	Penny Northcutt, RAC, FRAPS, CQA Regulatory Consultant for Fertility Focus REGSolutions, LLC Tel: 678-428-6978 Fax: 678-513-0937 Email: pennynorthcutt@theregsolutions.com
TRADE NAME:	Fertility Focus OvuSense Fertility Monitor
CLASSIFICATION NAME:	Device, fertility diagnostic, proceptive
DEVICE CLASSIFICATION AND PRODUCT CODE:	Pre-amendment, Unclassified Product Code: LHD
PREDICATE DEVICE NAME:	DuoFertility Monitor, K102499 Bioself 2000 Fertility Indicator, K904211

AUG 0 6 2013

SUBSTANTIAL EQUIVALENCE:
The Fertility Focus OvuSense Fertility Monitor is substantially equivalent to the legally marketed DuoFertility Monitor (K102499) and the Bioself 2000 Fertility Indicator (K904211). The Fertility Focus OvuSense Fertility Monitor has similar indications for use statements, principles of operation, and technological characteristics as the predicate devices.

DESCRIPTION OF THE DEVICE:
The Fertility Focus OvuSense Fertility Monitor is intended for measuring and recording core body temperature intra-vaginally on a nightly basis during the non-menstruating phases of the monthly female reproductive cycle. The Fertility Focus OvuSense Fertility Monitor consists of two components made of silicone - a Personal Sensor, which collects the data, and a Reader (with LCD display), which establishes a communication link to the Personal Sensor whereupon the data is transferred to the Reader.

Electromagnetic induction communications hardware transmits the stored temperature data from the Personal Sensor to the receiving device, the Reader, activated when the Sensor is placed on the Reader cradle and the Reader's dedicated download button is pressed. The microprocessor based Reader filters the overnight data, then calculates and stores the 25th percentile value, representative of the average basal (lowest) overnight temperature.

The Reader then displays these nightly temperature readings on a graph using a relative scale – the key information for necessary calculations being the temperature changes relative to other recorded temperatures within a cycle for a particular user, and not absolute temperature value. At the start of the next cycle, indicated by the User inputting first day of the bleeding in the cycle, the Reader algorithm calculates the date of ovulation in the prior cycle, and uses this to predict the fertile period for the cycle which has just started. The Reader then displays fertility information in a verbal summary, including:

- An indication of the day ovulation occurred in the prior cycle, or if ovulation was not detected it displays this information instead.
- An indication whether the cycle length was within the expected normal parameters.

INTENDED USE/INDICATIONS FOR USE:
The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

TECHNOLOGICAL CHARACTERISTICS:
OvuSense Fertility Monitor and DuoFertility Monitor have the following similar and substantially equivalent technological characteristics:

- Operating Principle – Both devices assess Basal Body Temperature.
- Temperature Sensor – Both devices use a thermistor sensor.
- Sensor Accuracy – The DuoFertility device has a quoted accuracy of +/- 0.05 degrees Centigrade, and of +/- 0.1 degrees Celsius; OvuSense Fertility Monitor has an accuracy of +/- 0.05 degrees Centigrade. Any potential difference in the accuracy of temperature measurements is not believed to raise any issues of safety, and is a function of the requirements of each devices' algorithms.
- User Inputs – Both devices have the facility for user input of relevant data.
- Display of Graphs – Both devices have the facility for the display of temperature graphs. The DuoFertility device uses a computer for this display and uses an absolute temperature scale, whilst OvuSense Fertility Monitor uses the OvuSense Reader for

display and a relative temperature scale. The different display methodologies do not raise any safety issues, with the relative temperature scale allowing the OvuSense Fertility Monitor user a graph view optimized to their particular temperature readings.

- Number of Measurements – Both devices record multiple temperatures. The difference in any relative number of temperature measurements is not believed to raise any issues of safety, and is simply a function of the requirements of each devices' algorithms.
- Automatic measurements – Both devices take measurements automatically.
- Wireless transfer of data – Both devices involve the transfer of data from the Sensor to a receiving unit.
- Algorithm – Both devices use an algorithm to calculate the date of ovulation. The additional information provided by the OvuSense Fertility Monitor device in respect of absence of ovulation and fertile period prediction is not believed to raise any direct issues of safety, and is employed for increased effectiveness.

The following differences between DuoFertility and OvuSense Fertility Monitor are noted and thus a secondary predicate or reference device – Bioself 2000 is used for substantial equivalence purposes.

- Number of Thermistors – The DuoFertility device uses two thermistors plus an accelerometer/movement Sensor; the OvuSense Fertility Monitor device uses a single thermistor. The Bioself 2000 device uses a single thermistor.
- Location of Thermistor – The DuoFertility device is worn on the skin; the OvuSense device is placed intravaginally by means of a Personal Sensor. The Bioself 2000 device can be used intravaginally or orally.

The use of two thermistors and an accelerometer (in DuoFertility) versus the use of a single thermistor (OvuSense Fertility Monitor and Bioself 2000) is not believed to raise any direct issues of safety or effectiveness, and the relative location of vaginal versus skin placement is employed by OvuSense Fertility Monitor and Bioself 2000.

NONCLINICAL PERFORMANCE TESTING:
A series of performance tests was conducted in support of the design verification of the Fertility Focus OvuSense Fertility Monitor.

Summary of Performance Testing Conducted on OvuSense	
Biocompatibility	In Vitro Cytotoxicity MEM Elution Assay
	Mucosal (Vaginal) Irritation Test
	Guinea Pig Maximization Sensitization Test
	USP Physicochemical Extraction Parameters
	ISO Acute Systemic Toxicity Test
	In Vitro Mouse Micronucleus Assay – 2 Extracts (ISO)
	In Vivo Mouse Micronucleus Assay – 2 Extracts
	Bacterial Mutagenicity Test (Ames Assay)

510(k) Summary

Summary of Performance Testing Conducted on OvuSense	
	Subchronic (14 day) Intravenous Toxicity Study in Non-Swiss Webster Mice (14 Repeat Dose Exposure)(GLP)
	Subacute (14 day) Intraperitoneal Toxicity Study in Non-Swiss Webster Mice (14 Repeat Dose Exposure) (GLP)
	Exhaustive Extractables
Electrical Testing	EN60601-1-4:2000 Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.
	EN60601-1-2:2007 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests
	EN301 489-3 v1.4.1 Electromagnetic Compatibility and Radio Spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3: Specific Conditions for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz
	IEC60601-1:2006 Medical equipment. Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
	EN302 291 v1.1.1 Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Close Range Inductive Data Communication equipment operating at 13,56 MHz; Part 2: Harmonized EN under article 3.2 of the R&TTE Directive
Mechanical Testing	Tensile (Pull Test)
Design Verification & Validation	Physical Dimensions, User Cleaning, Reliability for Operating Life, Human Factors-Machine Interface
Cleaning Validation	Cleaning Validation of Personal Sensor

CLINICAL TESTING:
Clinical investigation was conducted of the Fertility Focus OvuSense Fertility Monitor from 19 women who participated in a prospective study measuring 81 cycles over 3 months participation.

510(k) Summary

The data from the primary endpoint of the trial described in the CIP demonstrated that the OvuSense Fertility Monitor system of ovulation detection provided a biological and statistically significant improvement in ovulation detection compared with the traditional method of oral temperature measurement. It demonstrated good linear agreement with the gold standard detection of ovulation using ultra-sound and an improved 95% confidence interval for the agreement.

CONCLUSION:

Based on the nonclinical verification performance testing and clinical validation, it can be concluded that the Fertility Focus OvuSense Fertility Monitor is equivalent to the DuoFertility Monitor (K102499) and Bioself 2000 (K904211) with respect to intended use, principles of operation, and technological characteristics. The Fertility Focus OvuSense Fertility Monitor has been demonstrated to be as safe, as effective, and performs as well as or better than the predicates.

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

August 6, 2013

Fertility Focus, Ltd.
% Penny Northcutt, RAC, FRAPS, CQA
President/CEO
REGSolutions, LLC
717 Lakeglen Drive
Suwanee, GA 30024

Re: K122337
Trade/Device Name: Fertility Focus OvuSense Fertility Monitor
Regulation Number: None
Regulation Name: None
Regulatory Class: Unclassified
Product Code: LHD
Dated: July 30, 2013
Received: July 31, 2013

Dear Penny Northcutt,

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 contact 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. 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,

Glenn B. Bell -S

for Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

2. INDICATION FOR USE STATEMENT

Indications for Use

510(k) Number (if known): K122337

Device Name: **Fertility Focus OvuSense Fertility Monitor**

Indications for Use:

The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ AND/OR Over-The-Counter Use __X___
(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)

Glenn B. Bell -S

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K122337

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

August 6, 2013

Fertility Focus, Ltd.
% Penny Northcutt, RAC, FRAPS, CQA
President/CEO
REGSolutions, LLC
717 Lakeglen Drive
Suwanee, GA 30024

Re: K122337
Trade/Device Name: Fertility Focus OvuSense Fertility Monitor
Regulation Number: None
Regulation Name: None
Regulatory Class: Unclassified
Product Code: LHD
Dated: July 30, 2013
Received: July 31, 2013

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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.

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Sincerely yours,

Glenn B. Bell -S

for Benjamin R. Fisher, Ph.D.
Director
Division of Reproductive, Gastro-Renal,
and Urological 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: **K122337/S002**

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	Yunshang Piao -S 2013.08.06 15:22:04 -04'00'
Branch Chief Sign-Off	Elaine Blyskun -S 2013.08.06 15:50:00 -04'00'
Division Sign-Off *Acting DD for BRF*	Glenn B. Bell -S 2013.08.06 16:37:30 -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".
4/2/2013	M. McCabe Janicki	Edited sentence that starts "If you desire specific advice for your device on our labeling regulation (21 CFR Part 801)..." Replaced broken Compliance link with general link to DSMICA.
4/12/2013	Margaret McCabe Janicki	Fixed a typo: Paragraph 1, final sentence, "We remind you, however; that device labeling must be truthful..." Replaced incorrect semicolon with a comma.

cc: DCC - sign-off & original
ODE DRGUD/OGDB – (YSP)

DRAFT: YSP:8.6.2013
FINAL: YSP:clr:8.6.2013

2. INDICATION FOR USE STATEMENT

Indications for Use

510(k) Number (if known): K122337

Device Name: **Fertility Focus OvuSense Fertility Monitor**

Indications for Use:

The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ AND/OR Over-The-Counter Use __X__
(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)

Glenn B. Bell -S

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K122337

Welbon, James*

From: Welbon, James*
Sent: Saturday, August 10, 2013 11:56 AM
To: 'pennynorthcutt@theregsolutions.com'
Cc: DCCLetters
Subject: k122337 Correspondence
Attachments: k122337.pdf

Tracking:

Recipient	Delivery
'pennynorthcutt@theregsolutions.com'	
DCCLetters	Delivered: 8/10/2013 11:56 AM

5

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

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

May 07, 2013

FERTILITY FOCUS LTD
C/O REGSOLUTIONS, LLC
717 LAKEGLEN DRIVE
SUWANEE, GEORGIA 30024
ATTN: PENNY NORTHCUTT

510k Number: K122337

Product: OVUSENSE

Extended Until: 10/09/2013

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

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

1

Jones, Ashlee *

m:	Microsoft Outlook
	pennynorthcutt@theregsolutions.com
Sent:	Tuesday, May 07, 2013 3:27 PM
Subject:	Relayed: K122337 Extension Letter

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

pennynorthcutt@theregsolutions.com (pennynorthcutt@theregsolutions.com)

Subject: K122337 Extension Letter

2

fertility focus

May 6, 2013

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: K122337 OvuSense Fertility Monitoring System
Request for Extension to Request for Additional Information, Dated April 12, 2013

Dear Dr. Yun-shang Piao,

Fertility Focus would like to formally request a 180 day extension to the current hold for Premarket Notification K122337 OvuSense Fertility Monitoring System. We need this time to respond to all requested information.

If you have any questions or comments regarding this request, please contact me at 678-428-6978 (phone) or email to pennynorthcutt@theregsolutions.com.

Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

3

9

K122337 Vol. 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

October 17, 2012

FERTILITY FOCUS LTD
C/O REGSOLUTIONS, LLC
717 LAKEGLEN DRIVE
SUWANEE, GEORGIA 30024
ATTN: PENNY NORTHCUTT

510k Number: K122337

Product: OVUSENSE

Extended Until: 03/29/2013

Based on your recent request, an extension of time has been granted for you to submit the additional information we requested.

If the additional information (AI) is not received by the "Extended Until" date shown above, your premarket notification will be considered withdrawn (21 CFR 807.87(l)). If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the AI request.

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

Nichols, Karl *

From: Nichols, Karl *
Sent: Wednesday, October 17, 2012 4:16 PM
To: 'pennynorthcutt@theregsolutions.com'
Subject: K122337 Extension Letter
Attachments: CrystalViewerCAMA821C.rtf

K12

fertility focus

October 16, 2012

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to FDA Questions to K122337
OvuSense Advanced Fertility Monitoring System

Dear Dr. Luo,

Fertility Focus would like to formally request a 180 day extension to the current hold for Premarket Notification K122337 OvuSense Advanced Fertility Monitoring System. We need this time to respond to all requested information.

If you have any questions or comments regarding this request, please contact me at 678-428-6978 (phone) or email to pennynorthcutt@theregsolutions.com.

Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

fertility focus

October 16, 2012

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to FDA Questions to K122337
OvuSense Advanced Fertility Monitoring System

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Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

* * * COMMUNICATION RESULT REPORT (OCT. 5. 2012 11:39AM) * * *

FAX HEADER 1:
FAX HEADER 2:

TRANSMITTED/STORED : OCT. 5. 2012 11:36AM

FILE MODE	OPTION	ADDRESS	RESULT	PAGE
9808 MEMORY TX		678 513 0937	OK	9/9

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 Room –WO66-G609
Silver Spring, MD 20993-0002

Fertility Focus Ltd
% Penny Northcutt, RAC, FRAPS, CQA
President/CEO
REGSolutions, LLC
717 Lakeglen Drive
SUWANEE GA 30024

Re: K122337
Trade Name: OvuSense
Dated: July 31, 2012
Received: August 2, 2012

Dear Ms. Northcutt:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We cannot determine if the device is substantially equivalent to a legally marketed predicate based solely on the information you provided. To complete the review of your submission, we require the following additional information:

Indication for Use

1. Please revise your Indications for Use to include all versions of the devices (e.g, personal sensor only, reader only, starter pack) in the device name. Please modify the Indications for Use form, 510(k) Summary, and device labeling accordingly.

510(k) Summary

2. Please revise the 510(k) Summary and include the following information as required per 21 CFR 807.92:

   a. Provide a separate 510(k) Summary that clearly states "510(k) Summary" on the top of the first page;

   b. Update the Indication for Use shown to be identical to that requested in Deficiency No. 1 above;

   c. Describe in more detail the performance characteristics of the device, i.e., how the device functions;

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Fertility Focus Ltd
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President/CEO
REGSolutions, LLC
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SUWANEE GA 30024

Re: K122337
Trade Name: OvuSense
Dated: July 31, 2012
Received: August 2, 2012

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   b. Update the Indication for Use shown to be identical to that requested in Deficiency No. 1 above;

   c. Describe in more detail the performance characteristics of the device, i.e., how the device functions;

d. Provide a detailed comparison of the technological characteristics of the subject and predicate devices and justify any differences;

e. Describe the performance testing conducted on the subject device in greater detail, including electrical testing, biocompatibility testing, bench testing, and clinical validation testing.

Please note that we may request additional changes to your 510(k) Summary as we continue our review of your file.

Device Description

3. You did not provide sufficient information on device materials. Please provide a table summarizing each component used in the device, including the materials, the additives used (e.g., colorant) and their final concentrations (w/w), and the function of each component. In addition, please provide detailed information on each component (e.g., product name, CAS number, supplier, catalog number, Certificate of Analysis, Material Safety Data Sheet, etc.).

4. You indicated that the personal sensor is colored with a series of color masterbatches. Please work with the supplier to provide the following additional information:

a. Purity level of colorant

b. Estimated absolute amount of colorant (in weight) per device

c. Identification of other US legally marketed medical devices by device name, manufacturer, submission number, where the colorants have been previously used, if known

d. Toxicity risk assessment of this colorant that is preferably (b)(4) [redacted]

e. (b)(4) [redacted] (if known)

5. Your device description indicates that both the personal sensor and the reader have rechargeable batteries. Please provide more information on both sets of batteries (type, rated voltage, and capacity in mAH). Please clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just the batteries in the reader.

6. Please identify how the batteries are accessed. Explain how you keep the user from accessing the batteries.

7. You indicated that the vaginal personal sensor measures and records BBT data and transfer data to the reader via an electromagnetic induction link. It is not clear how the data is processed. You mentioned that BBT data is measured in (b)(4) [redacted]; therefore,

multiple data points are collected each night. It appears that the graphs and other data presented to the user include one BBT data point per night. It is not clear how this data point is derived. Please explain how this is done. Further, please provide information on how fertile days are derived from the data.

8. Further, explain whether any data is considered unusable, such as too low, too high, etc. How is this data handled? How are the data calculated when values are unusable or missing?

Software

9. We were unable to locate an adequate description of the software algorithm for OvuSense in your submission. Therefore, it is unclear how the OvuSense software uses the data collected from the Personal Sensor to calculate/estimate the day of ovulation. Other details of the software algorithm are also unclear, such as whether the software adjusts the algorithm as data on multiple cycles from a user accumulates. Please provide a clear description of the OvuSense software and how it uses data on continuous resting nocturnal vaginal temperature measurements to estimate the day of ovulation. Please also explain whether or not data from multiple cycles is used to adjust the estimate of the date of ovulation.

10. Your Hazard analysis indicates compliance of the battery charger with EN 60601-1 for mitigation of Energy Hazards (electric shock, burn, fire). However, this only ensures that the charger safely provides the power and/or trickle charge in a safe way; i.e., that the charger is electrically safe. This does not ensure that the entire device is electrically safe. Please revise your Hazard analysis to reflect all mitigations to address electrical shock, burn, fire, explosion, and battery leakage. Also address both sensor and reader interface with the user.

11. Your document titled "System Acceptance Test & Trace Specification" is identified as fulfilling the requirement for a traceability analysis/matrix document. This document includes a table that provide a requirement identification number (format xxx_xxx_###) and identification of the corresponding test number (format test##). However, this document does not include any reference to hazards. Further, the hazard analysis does not appear to include reference to requirements or software tests. The reference number included in the hazard analysis chart uses a format (x.x) that does not correspond to any numbers we can identify. Also, no test ID numbers are included. Thus, the hazards are not tied to tests in the hazard analysis or the traceability analysis.

    While we understand that not all hazards will have a correlating software test, the functional failure hazards should include some software testing (specifically identified). All or most of the hazards should have a correlation to the requirements. Please explain where this is provided in the documentation we have or provide an additional document that shows correspondence between all of the following: requirements, testing, and hazards.

12. Your software revision level history only indicates that the current version is version 1.3. Please identify previous versions (developmental versions) and a brief description of difference with each version

Electricity Safety and Electromagnetic Compatibility Testing

13. General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. Please explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

14. Please explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this related to use with a DC power supply or batteries?

15. The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. Please explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply or to the batteries, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

Material Safety Testing

16. (b)(4) testing was included in your submission to support the biocompatibility of the patient contacting portions of your proposed device. The test methods identified would be supportive of a device with limited contact with mucosal tissues. However, the proposed device will be used daily for up to 21 days per month and may be used for many months. Therefore, this device could be considered a permanent implant in contact with mucosal tissue. Per FDA Bluebook memo G95-1, testing to support long-term use of the device would include (b)(4)

17. You indicated that the personal sensor is colored with a series of color "masterbatches". Please clarify if you plan to market one or multiple color versions of the sensor. If more than one color sensor is proposed, independent biocompatibility testing will be needed to support each color version proposed, unless you can show that the identical materials (supplier, catalog number, colorants, mold release agents, contact potential, etc.) have been used in a 510(k)-cleared device. (b)(4) [redacted]

Performance Testing- bench

18. Please provide mechanical testing to assess (b)(4) [redacted]

Performance Testing-Clinical

19. Of the three sections in your submission discussing the clinical validation study (Section 10, Attachment M and Attachment R), none explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined (b)(4) [redacted] (b)(4) [redacted]. The only actual data provided were (b)(4) [redacted]. No other information was provided to support the conclusion that the OvuSense predicted the day of ovulation with greater accuracy compared to the once-daily oral BBT. (b)(4) [redacted]. In order for FDA to independently verify your conclusion regarding the relative performance of OvuSense vs. oral BBT measurement, please provide all line data for each subject. Also, please provide a statement of your pre-specified statistical hypothesis test and definition of study success. (b)(4) [redacted]

20. Your study plan as described in Attachment M refers to Freundl *et al.* (2003) and Colombo and Masarotto (2000) as the basis for study methodology for comparing the OvuSense vs. BBT. Freundl *et al's* (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. Please explain why you believe these two references are appropriate as the basis for the study design. Please also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of ovulation as a gold standard to support the proposed Indication for Use.

21. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, you state that the results (b)(4) [redacted]

22. The OvuSense is the first extended use vaginal probe for basal body temperature measurement. It is important, therefore, that you demonstrate the probe does not cause pain, discomfort, bleeding, etc. In Attachment R, you have stated "No adverse effects were reported" in the clinical validation study. Your submission does not describe, how safety was evaluated in the clinical validation study of the OvuSense. Please explain how safety information was obtained to support their conclusion.

Labeling

23. You have provided the primary and underside labeling for both the OvuSense Sensor and Reader in the submission. Please revise the labels as follows:

    a. Add storage conditions;

    b. Add lot number and expiration date;

    c. The label includes a number of unrecognized symbols; please add text directly next to each symbol on the primary and underside labels for both the OvuSense sensor and reader;

    d. Include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"** to both labels.

24. Please make following changes to the User Manual:

    a. Add a separate Device Components Section at the beginning of the User Manual that lists all components of the device;

    b. Add a separate Warnings and Precautions Section at the beginning of the User Manual that includes Warnings and Precautions that are currently located throughout the User Manual;

    c. Please include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"** in an individual text box in a prominent location on the front of the User Manual;

    d. Add a separate Direction for Use Section that instructs the user explicitly, step-by-step, how to operate the device that is currently located throughout the User Manual;

e. On page 3 of the User Manual, you stated that the user could recycle the used reader and sensor. The sensor is a personal, single user device with a 3 month use-life. The reader does not have an expiration date or use-life. Please state explicitly if the reader is a single user device and how long the use-life is;

f. On pages 6 of the User's Manual you stated that "If you do not have a regular cycle length, OvuSense may still provide you with information about your menstrual cycle and timing of ovulation." Please provide data to substantiate this claim, or remove this claim from device labeling;

g. The personal sensor is an intra-vaginal, tampon-shaped device. On Page 13, you mentioned there may be a small risk of toxic shock syndrome, a rare condition caused by the growth of *Staphylococcus aureus* on blood or fluids in the vagina. Because the user may not be familiar with this medical emergency, please provide detailed explanation of the disease and include all warning signs. Please consider using the information from 21 CFR 801.430 (d), which is the regulation for menstrual tampon labeling;

h. On Page 25, you stated that "the OvuSense Scales graphs using relative temperature points for each cycle." Please clarify what this means and how relative temperature points are related to the BBT;

i. On Page 33, you stated that "if you experience... discomfort, irritation, or a vaginal discharge during use of the personal sensor, stop using to the personal sensor immediately and consult your doctor." This statement seems to be contradicted to your statement of "No adverse effects were reported" in the clinical validation study. Please clarify the discrepancy;

j. The label includes a number of unrecognized symbols; please add text directly next to each symbol used in the labels.

Please note that we may identify additional labeling deficiencies following review of your updated labeling and your responses to the questions in this additional information letter.

Administrative Requirements

25. Please provide Standards Data Report for 510(k) Forms (Form 3654) for all the standards you referenced to complete the performance testing requested in this review memo. You can access this from using the following link: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM081667.pdf.

26. Your 510(k) did not include the Certification of Compliance with Requirements of the ClinicalTrials.gov Data Bank (Form 3674). Effective December 26, 2007, all firms submitting a 510(k) are required to submit Form 3674 regarding registration of applicable clinical trials in the Clinical Trials Data Bank (http://prsinfo.clinicaltrial.gov). Form 3674 can be obtained by going to the following web address:

http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf. Please submit Form 3674 for review.

The deficiencies identified above 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 (Act) for determining substantial equivalence of your device.

You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(l), and you have received a letter from FDA allowing you to do so. If you market the device without conforming to these requirements, you will be in violation of the Act. You may, however, distribute this device for investigational purposes to obtain clinical data if needed to establish substantial equivalence. Clinical investigations of this device must be conducted in accordance with the investigational device exemption (IDE) regulations (21 CFR 812).

If the information, or a request for an extension of time, is not received within 30 days, we will consider your premarket notification to be withdrawn and your submission will be deleted from our system. If you submit the requested information after 30 days it will be considered and processed as a new 510(k) (21 CFR 807.87(l)); therefore, all information previously submitted must be resubmitted so that your new 510(k) is complete. For guidance on 510(k) actions, please see our guidance document entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089738.pdf. The purpose of this document is to assist agency staff and the device industry in understanding 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 and Modernization Act.

If the submitter does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request.

The requested information, or a request for an extension of time, should reference your above 510(k) number and should be submitted in duplicate to:

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

If you have any questions concerning the contents of the letter, please contact Dr. Michelle T. Luo, at (301) 796-5314. If you need information or assistance concerning the IDE regulations, please contact

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 Elaine H. Blyskun
Chief, Obstetrics and Gynecology
Devices Branch
Division of Reproductive, Gastro-Renal,
and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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

COVER SHEET MEMORANDUM

From: Reviewer Name Michelle

Subject: 510(k) Number K122387

To: The Record

Please list CTS decision code AI

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/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?			X
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/eRoomReq/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?			X
Is clinical data necessary to support the review of this 510(k)?		X	
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			X

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**
	Unclassified	LHD

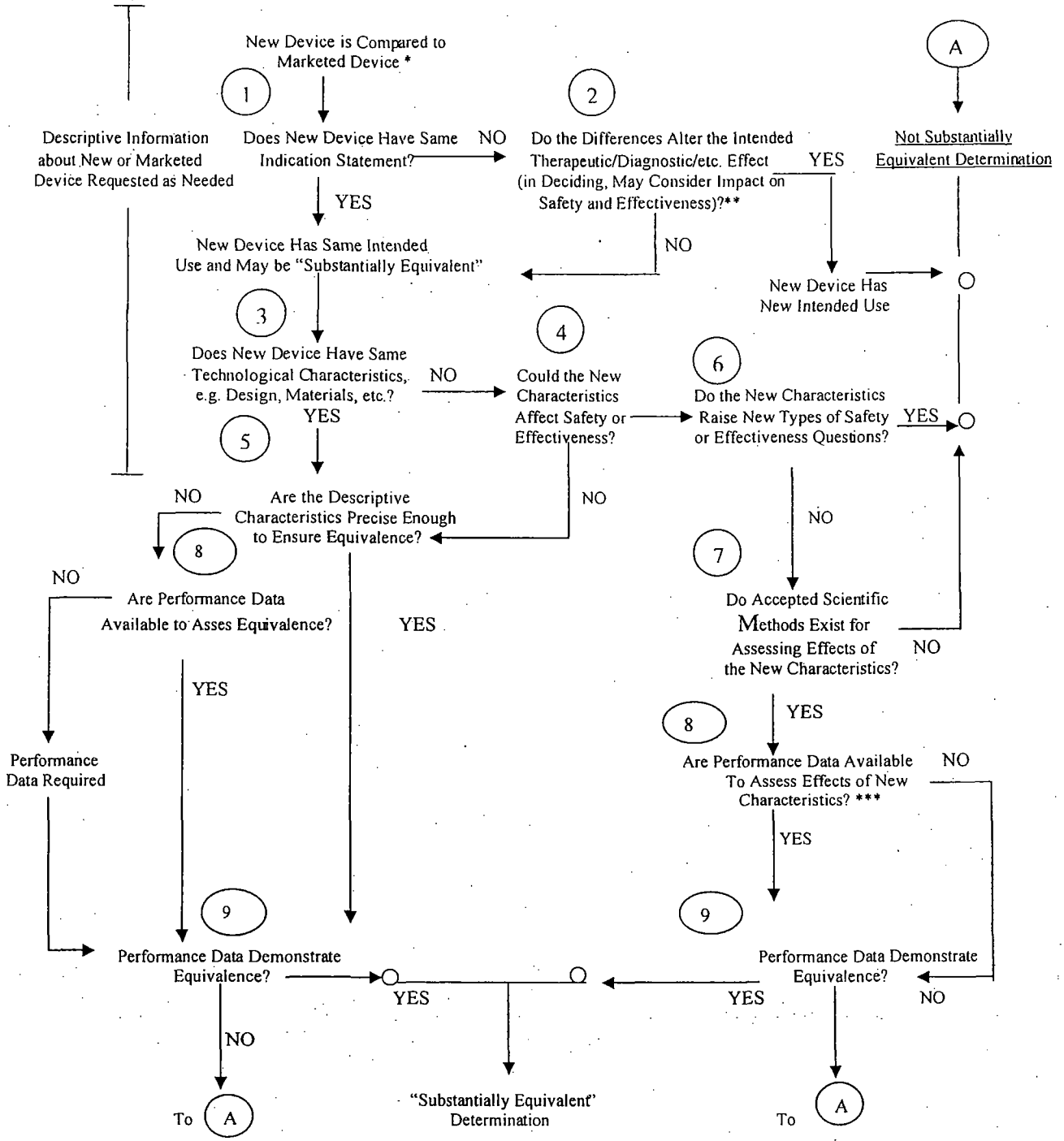
(*If unclassified, see 510(k) Staff)

Additional Product Codes: _____

Review: _____ _____ _____
(Branch Chief) (Branch Code) (Date)

Final Review: _____
(Division Director) (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 **MEMORANDUM**

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

Premarket Notification [510(k)] Review
Traditional

K122337

Date:	October 02, 2012	**Office:**	ODE
To:	The Record	**Division:**	DRGUD
From:	Michelle Luo, PhD, Biologist	**Branch:**	OGDB

510(k) Holder:	Fertility Focus, Ltd
Device Name:	OvuSense Advanced Fertility Monitoring System
Contact:	Mo, Aslam, Ph.D
Address:	Unit 19D, University of Warwick Science Park, Warwick Technology Park
Phone:	(044)- 1494-510272
Email:	mo.aslam@fertility-focus.com

I. Purpose and Submission Summary

The 510(k) holder would like to introduce the OvuSense Advanced Fertility Monitoring System device into interstate commerce.

The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

This is the first round of review of this submission. The sponsor will need to revise the 510(k) Summary, and labeling, provide additional information regarding device description, software and electrical safety testing, clinical testing, and sterilization/cleaning validation, before a substantial equivalence determination can be made.

Julia Corrado, Medical Officer, ODE/DRGUD/OGDB, provided clinical consultation. Kathy Daws-Kopp, Electrical Engineer; ODE/DRGUD/OGDB, provided consultation review on the software and electrical saftety. Haijing Hu, Microbiologist, ODE/DRGUD/OGDB, provided consultation on the sterilization. Sharon Andrews, Biomedical Engineer, provided review guidance for this submission.

II. Administrative Requirements

	Yes	N	N/A
Indications for Use page (Indicate if: Prescription or OTC)	x		
Truthful and Accuracy Statement	x		

	Yes	N	N/A
510(k) Summary	x		
Standards Data Report for 510 (k) Form (Form 3654)	x		
ClinicalTrials.gov Data Bank Form (Form3674)		x	

Indications for Use Form

The sponsor has provided the Indications for Use form. The Indications for Use Form is consistent with the predicate device cleared by FDA as described in Section IV – Indications for Use.

Truthful and Accuracy Statement

The sponsor provided a signed Truthful and Accuracy Statement.

510(k) Summary

The sponsor provided 510(k) Summary and they need to revise as follows and include the information required per 21 CFR 807.92:

a. Provide a separate 510(k) Summary and clearly stated "510(k) Summary" for the title on the top of the first page on your letter head paper;

b. Provide the revised Indications for Use statement as requested in Deficiency No. 1;

c. Describe in more detail in the device description and provide performance characteristics of the device, such as the material used for each component of the device, and how the device functions;

d. Provide a detailed comparison of the technological characteristics of the subject and predicate devices and justify any differences; and

e. Describe the performance testing conducted on the subject device in greater detail, including the electrical testing, software validation, biocompatibility testing, and bench testing.

Standards Data Report for 510(k) Form

The submission contains Standards Data Report form (Form 3654) for the following FDA-recognized standards:

- ISO 14971 2007 Application of Risk Management to Medical Devices
- IEC 62304-2006 (Medical Device Software - Software Life Cycle Processes)
- ISO 10993-5:2003 Biological Evaluation of Medical Devices, Part 5 – Tests for In Vitro Cytotoxicity

- ISO 10993-10:2006 Biological Evaluation of Medical Devices, Part 10 – Tests for Irritation and Delayed-Type Hypersensitivity
- ISO14155: 2011 Clinical investigation of medical devices for human subjects - Good clinical practice.
- ASTM E1112: 2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature
- IEC 60601-1 (Medical Electrical Equipment - Part 1: General Requirements for Safety) Standard: Electromagnetic Compatibility Requirements and Tests)

The firm also states that the device was developed in conformance with the following standards that are not FDA recognized:

- EN 60601-1-2 (Medical Electrical Equipment, Part 1-2: General Requirements for Safety – Collateral Standard: Electromagnetic Compatibility Requirements and Tests)
- EN 60601-1-4 (Medical Electrical Equipment, Part 1-4: General Requirements for Safety – Collateral Standard: Programmable Electrical Medical Systems)

The lists are incomplete. The sponsor should provide Standards Data Report (From 3654) for additional standards in response to this deficiency letter referenced in this submission.

- ISO 10993-1 (Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing with a Risk Management Process)
- IEC 60601-1-11 (Medical Electrical Equipment, Part 1-11: General Requirements for the Safety - Collateral Standard: Requirements for Medical Electrical Equipment and Medical Electrical Systems Used in the Home Healthcare Environment)

ClinicalTrials.gov Data Bank Form (Form 3674)

The firm has not submitted the Form 3674, Certification of Compliance with Requirements of the ClinicalTrials.gov Data Bank. They are required to submit this form.

III. Device Description

	Y	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)?	x		
Are "cleaning" instructions included for the end user?	x		

Basal body thermometers are pre-amendment unclassified medical device, product codes LHD. The sponsor is required to submit a traditional 510(k) for clearance.

The OvuSenseDevice is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception). The sponsor stated that the principlesof device function is measuring BBT via vagina overnight (b)(4) (b)(4), during the non-menstruating period of a woman's cycle. The device records and analyzes large quantities of BBT data and applies a software algorithm to calculate monthly cycle of ovulation.

It is noted that OvuSense is the first extended use vaginal probe for BBT measurement. The OvuSense consists of the following components:

1. Personal Sensor: a non-sterile, battery-operated, tampon-shaped vaginal insert, as shown as Figure 4.1. 3 below. It has a tail part sealed with the main base. It consists of an (b)(4) and RF communications circuitry. Every night it is cleaned and inserted into the vagina and left in place overnight for up to 12 hours. The sensor readings are taken (b)(4) to record basal body temperature, (b)(4). The device is removed in the morning, cleaned and placed on the cradle where the data is downloaded to the reader. The sponsor stated that a single personal sensor can be used for three months/cycles, and is replaced by a new one. The personal sensor has a temperature measuring range of 35.5-42.0 C.

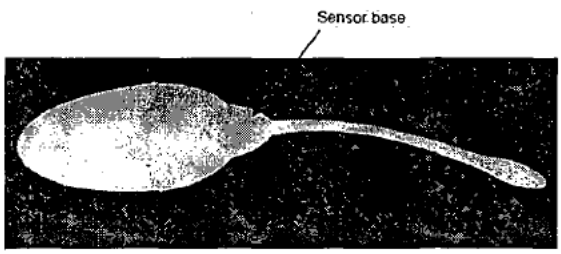


FIGURE 4.1-3: Personal Sensor Showing Base

2. Reader: the unit receives and stores BBT data from the vaginal sensor via an electromagnetic induction link, provides information on an LCD display and storage place for the personal sensor during the day when not in use. It is rechargeable battery operated and has a back up a/c power plug. The reader has seven modes of operation: standby, power-on/self-test, download, idle, setup, input and display mode. It serves as a master device by establishing communications with the personal sensor with "download" button key press by the user.

3. User Interface: consists of an LCD display, five buttons, and software menu-driven screens which allow the user to interact with the reader and view status information.

4. Software: Application software which calculates and displays user-interface menu screens on the LCD display of the Reader. Software runs on a (b)(4).

The sponsor provided the engineering drawings in the submission and the picture and dimensions of the subject device as follows:

Personal sensor: 4.5 x 1.0 x 0.4 inch
Reader: 7.0 x4.0 x1.25 inch
LCD screen reader: 2''x 1.5''

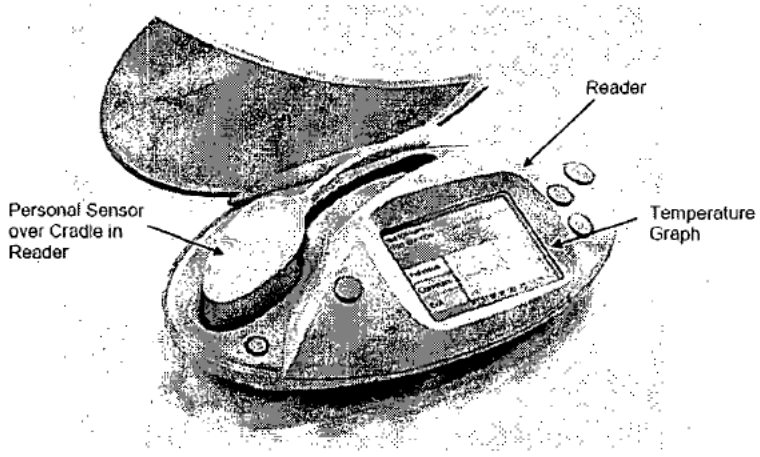


FIGURE 4.1-1: OvuSense Fertility Monitoring System

Both personal sensor and reader are operated by rechargeable batteries. The sponsor needs to provide more information on both sets of batteries, (type, rated voltage and capacity in mAH) and how they are accessed. The sponsor should clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just in the reader.

The sponsor stated the data is collected in (b)(4) are collected each night, it appears that the graphs presented to the user include only one data point indicating the BBT per night. It is not clear how the data is processed. Ms. Kathy Daws-Kopp discussed this issue in her software consultation. Dr. Julia Corrado raised the same question in her clinical review. The sponsor will be asked how BBT data point is derived from the graph presented on the reader. (see Section IX software review for additional details)

The sponsor also listed the materials used for the device summarized in the following table 1. The personal sensor which directly contacts with the woman's vagina is made of (b)(4) (b)(4). The reader and cradle are made of plastic casing which does not contact with patients. The sponsor should provide detailed information on the material of each component (e.g., product name, CAS number, supplier, catalog number, Certificate of Analysis, Material Safety Data Sheet, etc.).

Table 1 OuvSense systems Materials

Components	Material	Patient contact
Personal Sensor	(b)(4)	Direct
Room Temperature Vulcanizing (RTV) Seal	(b)(4)	Direct
Epoxy Coating	(b)(4)	Direct

Color Master Batch for personal sensor	(b)(4) [redacted]	Direct
Reader Cradle	(b)(4) [redacted]	Indirect
Reader	(b)(4) [redacted]	Indirect

The sponsor stated that sensor is also colored with a series of color masterbatches. The sponsor will be asked to provide to provide the following additional information: purity level of colorant; estimated absolute amount of colorant (in weight) per device; identification of other US legally marketed medical devices by device name, manufacturer, submission number, where the colorants have been previously used, if known; toxicity risk assessment of this colorant that is preferably (b)(4) [redacted] (if known).

IV. Indications for Use

From the Indication for Use (IFU) form for OvuSence:

The OvuSence is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

TheIndication forUse is similar to the predicates.

Per OGDB current practice, the sponsor should include all versions of the devices (e.g, personal sensor only, reader only, starter pack) in the device name in the IFU form

V. Predicate Device Comparison

The sponsor identified Bioself 2000 (K904211) device as the predicate described below. Comparative information between the subject device and the predicate is provided in the submission.

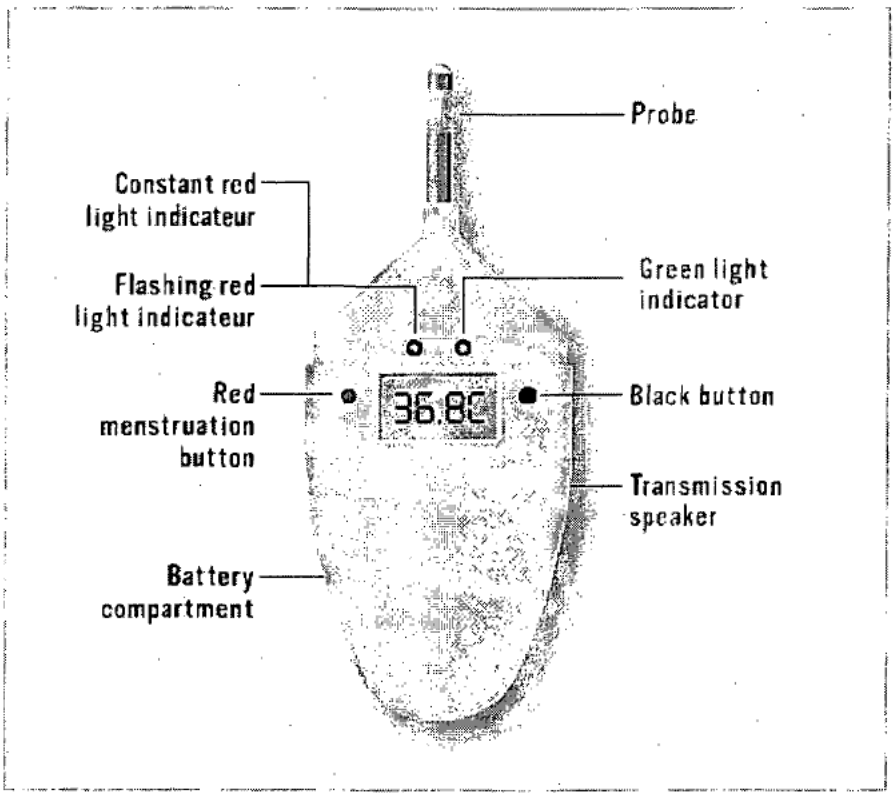
Intended Use: The Bioself 2000 Fertility Indicator is an aid in measuring and identifying basal body temperature (BBT) in a woman's menstrual cycle in order to achieve conception. The device is not be used for contraception.

Technology: Bioself is a small hand held, microprocessor controlled, portable electronic thermometer to measure the basal body temperature. It can be used by the mouth, the rectum or the vagina and is composed of the following compartments:

1. probe: record BBT temperature daily in the morning;
2. three indicator lights that tell the user daily level of fertility: green light indicates the infertile phase of menstrual cycle; a red light to record the beginning of the period, a black push button to access to recorded data;

3. a LCD which the user reads temperature everyday;
4. batteries compartment: 3 alkaline 1.5V batteries;
5. transmission speaker; transmit all the data stored in the memory of the device to a Bioself centre and have it printed out as a graph

Here is the picture of the predicate device:



The following table listed the details regarding to technological characteristics for the subject and predicate devices.

Category	OvuSense (Subject device) K122337	BioSafe 2000 (Predicate Device) K904211
Intended Use	The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).	The Bioself 2000 Fertility Indicator is an aid in measuring and identifying basal body temperature (BBT) in a woman's menstrual cycle in order to achieve conception. The device is not be used for contraception.
	• Measure BBT via vagina continuously overnight (b)(4) during	• Measure BBT via vagina, mouth, or rectum via

Principles of operation	non-menstruating period of a woman's cycle; • Uses the data and software algorithm to predicate a woman's ovulation pattern	manual measurement upon waking in the morning;
Material	Sensor: (b)(4) Reader: plastic casing	Probe: metal Body: plastic casing
Time needed to take the BBT	12 hours, overnight	2 minutes, in the morning
BBT measurement method	Continuously taking BBT in (b)(4) (b)(4) overnight, (b)(4)	single measurement, taken when waking in the morning
Biocompatibility testing	Following tests were assessed based on ISO 10993: 2009 • (b)(4)	No tested
Data transfer method	RF communication circuit	none
Single use device	Sensor: single use, multiple-use ((b)(4)	Single use
Energy use	Rechargeable batteries/ AC connector	3 standard alkaline batteries
Sterilization	Clean, non-sterile,	Clean, non-sterile
Shelf life	2 years	Not mentioned

Substantial Equivalence Discussion

Intended Use

The Bioself 2000 Fertility Indicator is an aid in measuring and identifying basal body temperature (BBT) in a woman's menstrual cycle in order to achieve conception. The device is not be used for contraception.

The Intended Use for subject device is similar as the predicate.

Technological Characteristics

Both the OvuSense (subject device) and Bioself 2000 fertility indicator (predicate device) are designed to measure basal body temperature (BBT) using a probe, and to predict a woman's ovulation pattern.

However, the subject device has significant differences in design compared to the predicate: the subject device is the first extended use vaginal probe for BBT measurement. It measures BBT by a sensor via vagina continuously overnight (b)(4) during non-menstruating period of a woman's cycle, and generating (b)(4) in a 12 hours period. Following the wearing period, data is transferred by RF communication from sensor to the reader and applied a software algorithm processed. The predicate measures BBT by a thermoster probe via vagina, mouth, or rectum and taking one single manual measurement upon waking in the morning. The user reads BBT immediately.

The materials for patient directly-contacting part are different: the personal sensor of the subject is made of silicone, sealed by silicon adhesives, and coated by thermostor; the probe for the predicate is made of metal. There are also other differences for the subject device, e.g., limited (b)(4) use-life and clean process. These new characteristics could affect the safety and effectiveness, However, it does not raise new types of safety and effectiveness questions, because we have cleared continuously measure BBT monitor before (DuoFertility conception monitor, K102499), and differences in BBT testing methods, use-life, and cleaning & reprocess are common for the BBT monitors 510 (k) submissions.

Accepted scientific methods exist to address this difference in technological characteristics, (e.g., software validation, performance testing, biocompatibility, clean validation, clinical testing). A clinical study using the subject to accurate directly BBT comparing with other methods, especially ultrasound detection of follicular ovulation as the gold standard, is essential for BBT submission, At this point, the sponsor has not provided adequate testing data regarding software validation, biocompatibility, performance testing, clean validation and clinical study. They need to provide the performance data before a substantial equivalence determination can be made. See section VII (sterilization), VIII (biocompatibility), IX (software), X (Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety), XI (performance testing), XIV (performance testing-clinical) for details.

VI. Labeling

The sponsor has provided a user manual, the primary and underside labeling for both OvuSense sensor and reader in the submission.

The sponsor stated the symbols used in the labeling conform to standard ISO 15223:2007, Medical Device, Symbols to be used with Medical Device labels, labeling, and information to be supplied Part 1 – General Requirements. However, ODE does not recognize this standard. The sponsor is required to add text to explain those symbols.

The sponsor needs to revise the reader and sensor labels as follows:

1) Add storage conditions;
2) Add lot number and expiration date;
3) Add text directly next to each symbol on primary and underside labels for both OvuSense sensor and reader.
4) Include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"**

The sponsor should make following changes to the User Manual:

1) Add a separate Device Components Section at the beginning of the User Manual that lists all components of the devices;

2) Add a separate Warning Section at the beginning of the User Manual that includes Warnings and Precautions that are currently located throughout the User Manual.

3) Please include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"** In an individual text box in **a** prominent location on the front of the User Manual.

4) Add a separate Direction for Use Section that instructs the user explicitly, step by step, how to operate the device that is currently located throughout the User Manual.

5) On pages 6, the User's Manual the sponsor states that "If you do not have a regular cycle length, OvuSense may still provide you with information about your menstrual cycle and timing of ovulation." Please provide data to substantiate this claim, or remove this claim from device labeling.

6) The personal sensor is an intra-vaginal, tampon-shaped device. On Page 13, the sponsor listed that there may be a small risk of toxic shock syndrome, a rare condition caused by the growth of *Staphylococcus aureus* on blood or fluids in the vagina. Because the user may not be familiar with this medical emergency, please provide detailed explanation of the disease and include all warning signs. Please consider using the information from 21 CFR 801.430 (d), which is the regulation for menstrual tampon labeling.

7) On Page 25, the sponsor stated that "the OvuSense Scales graphs using relative temperature points for each cycle". Please clarify what it does mean, how this relative temperature points related to the BBT.

8) The label includes a number of unrecognized symbols; please add text directly next to each symbol used in the labels.

We may identify more labeling deficiencies and will continue to revise the labeling while reviewing new data.

VII. Packaging/Sterilization/Shelf Life/Reuse

Packaging

The device is packaged in three configurations:

- personal sensor only; packed in double packaging of Tyvek pouch inside of white marketing carton box inside of a shipping carton;
- reader only; double-wrapped in bubble wrap inside of white marketing carton box inside of shipping carton;
- personal sensor and reader-advanced fertility monitoring system together both in Tyvek pouch inside of a white marketing carton box inside of shipping carton

The is an acceptable package .

Sterilization/Reuse

The sensor of the OvuSense is provided clean, non-sterile. The sponsor provides the instructions for the user to clean the device and recommended that the user thoroughly clean the sensor before and after each use and stores it in the cradle on the reader when not in use. The sponsor mentioned that the sensor was a

personal, single user device with (b)(4). The sponsor provided the cleaning validation test and used bioburden as a marker to validate the cleaning procedure for the sensor. (b)(4) Although, FDA does not accept bioburden as a marker for cleaning validation, OGDB does not require strict cleaning validation for certain single user vaginal devices. Therefore, we will not require the company to re-conduct the cleaning validation with another marker.

Shelf Life

The sponsor has specified the shelf life for the device is 2 years. Because the shelf life test of the predicate device is not reported, the sponsor is not required to conduct the shelf life test for the subject device.

Haijing Hu, Microbiologist, ODE/DRGUD/OGDB conducted the detailed review of this Section and recommended the deficiencies based on the analysis. (Review memo attached.)

VIII. Biocompatibility

The personal sensor of the proposed subject device contacts with woman's vagina for approximately 12 hours overnight daily. As shown in the Table 1, the sensor is colored, made of silicone, sealed by silicon (b)(4). In accordance with ISO 10993-1:2003 Biological Evaluation of Medical Devices, Part 1, evaluation of the (b)(4) potential of the subject device is needed.

The sponsor conducted and submitted the protocols and results of the following biocompatibility studies evaluating the subject device. They stated that all testes were conducted at WuxiAppTec under GLP.

- (b)(4)

The sponsor stated that all sample preparation procedures have compliant with those outlined in ISO 10993-12:2007. (b)(4). This is a stand alone test which FDA usually do not required for the biocompatibility test. .

Cytotoxicity

(b)(4)

(b)(4)

Sensitization

(b)(4)

(b)(4) Study

(b)(4)

IX. Software

The subject device runs the software language (b)(4) on a (b)(4). The software controls the user interface, interfaces between sensor and reader, and processes the data collected by the sensors.

Device software was reviewed by Kathy Daws-Kopp, Electrical Engineer; ODE/DRGUD/OGDB. Below table are key finds from her review.

The major software concern from Ms. Daws-Kopp is that how the data is processed. The sponsor stated the data is collected in (b)(4). (b)(4), it appears that the graphs presented to the user include only one data point indicating the BBT per night.

Dr. Julia Corrado raised same question in her clinical review. The sponsor will be asked how BBT data point is derived from the graph presented on the reader. The sponsor should also provide information on how fertile days are derived from the data.

Version: Version 1.3		
Level of Concern: They identify the level of concern as minor and we agree		
	Yes	**No**
Software description: Section 5.2	✓	
Device Hazard Analysis: Section 5.3	✓	
Software Requirements Specifications (Summary only): Section 5.4	✓	
Architecture Design Chart: not required for minor	NA	
Design Specifications: not required for minor	NA	
Traceability Analysis/Matrix: Section 5.5	✓	
Development: not required for minor	NA	
Verification & Validation Testing: Section 5.6	✓	
Revision level history: Section 5.7	✓	
Unresolved anomalies: not required for minor	NA	

Further, they should clarify what the data is considered unusable, such as too low, too high, etc. How this data is handled and calculated when values are unusable or missing.

Ms, Daws-Kopp raised several other questions regarding to the software hazard analysis and revision level history. The sponsor will be asked for additional information on those questions. (complete consulting review is attached.)

X. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

Electrical safety and EMC information was reviewed by Ms. Daws-Kopp (memo is attached)

The sponsor conducted electrical safety testing and EMC information and lists the standards which was compliant when conducting the tests. . Ms. Daws-Kopp provide the consult review and concluded that the testing appears to sufficiently address EMC, except following questions will be sent to the sponsor for additional information:

General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. The sponsor needs to explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

The sponsor needs to explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this related to use with a DC power supply or batteries?

The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. The sponsor needs to explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply or to the

batteries, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

XI. Performance Testing – Bench

The sponsor stated that they performed the verification testing for the Fertility Focus OvuSense and the device complies with the requirements of ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature. The sponsor submitted the testing report for review. Temperature range, accuracy and stability of temperature parameters were performed on five devices. The results showed the device can meet the following performance specifications:

(b)(4) [redacted]

The above specification is acceptable. Because the personal sensor has egg and tail two parts and is sealed by adhesives, the sponsor should provide mechanical testing to assess (b)(4) [redacted]

XII. Performance Testing – Animal

This section does not apply to this submission.

XIII. Performance Testing – Clinical

The company sponsored a clinical trial to investigate the efficacy of an indwelling temperature monitor to identify ovulation and to predict the fertile period. OvuSense, consisting of the vaginal, indwelling temperature data logger (Personal Sensor) and a Reader were used in the study. Ultrasound to determine ovulation by follicular size was used as a confirmation of ovulation.

This was a prospective, non randomized, longitudinal, observational, open label study at a single site.

The study consisted of comparative measurements of BBT established with three positive controls: single point, oral temperature using a digital thermometer; positive luteinizing hormone results obtained using Clearblue urine testing strips; and results from the OvuSense system in conjunction with ultrasound foliculometry.

(b)(4) [redacted]

Patient **Inclusion Criteria**

- Age 20-37
- Cycle length 26 - 36 days

- BMI 19 - 29
- Must not have used oral contraception or hormonal treatments, nor have been lactating for two previous cycles
- Must not be taking any regular medication which could alter BBT, cycle or ovulation
- Must pass an inspection for vaginal health (including swab and screen for Chlamydia)
- Signed Informed Consent
- Available for ultrasound scan for up to three consecutive days at around the time of ovulation
- less than three miscarriages

Exclusion Criteria

- Known abnormal ovulation, abnormal cycles
- Age < 20 or >37
- Reported cycle length outside of range of 26-36 days
- Use or oral contraception, hormonal treatments or lactating within two previous cycles
- Taking regular medication which could alter BBT, cycle or ovulation
- Failure at inspection for vaginal health
- abnormal patterns of sleep or shift worker
- three or more miscarriages

19 women who met the study criteria contributed a total of 81 cycles. The differences (in days) between the oral temperature and ultrasound and between the OvuSense and ultrasound estimated day of ovulation were calculated. Of these, (b)(4) [redacted]

Dr. Corrado provided the clinical review and raised the clinical issues as follows (complete review memo is attached):

1. The sponsor has not explained the software algorithm for OvuSense. It is unclear how the software uses the data collected from the Personal Sensor to calculate the day of ovulation. It is also unclear whether the software adjusts the algorithm as data on multiple cycles from a user accumulates.

2. None of the sections describing the clinical study explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined by the (b)(4) [redacted] This is a fundamental information deficit in this submission.

3. The study plan refers to Freundl et al (2003) and Colombo and Masarotto (2000) as the basis for study methodology for comparing the OvuSense vs. BBT. Freundl et al's (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. The sponsor should explain why he believes these two references are appropriate as the basis for the study design. He should also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of

ovulation as a gold standard to support the proposed Indication for Use.

4. The discussion of study results in Attachment R did not provide any details of data from study subjects that would allow FDA to independently verify the study conclusions. The only data provided were (b)(4) [redacted]. No other information was provided to support the conclusion that the OvuSense predicted the day of ovulation with greater accuracy compared to the once-daily oral BBT. (b)(4) [redacted]

5. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, the sponsor states that the results (b)(4) [redacted]

6. The sponsor has not explained how safety was evaluated in the clinical validation study of the OvuSense. The final report merely states "No adverse effects were reported." The sponsor needs to explain how safety information was obtained to support their conclusion.

The sponsor will be asked to provide additional information per Dr. Corrado's review comments.

XIV. Deficiencies

Please see attachment.

XV. Contact History

No contact history.

XVI. Recommendation

Additional information needed.

Regulation Number: None
Regulation Name: None
Regulatory Class: Unclassifed
Product Code: LHD

Michelle T. Luo, Biologist, OGDB — 10/01//2012 Date

Elaine Blyskun, Branch Chief, OGDB — Date

Attachement:--Deficiencies

Indication for Use

1. Please revise your Indications for Use to include all versions of the devices (e.g, personal sensor only, reader only, starter pack) in the device name. Please modify the Indications for Use form, 510(k) Summary, and device labeling accordingly.

510(k) Summary

2. Please revise the 510(k) Summary and include the following information as required per 21 CFR 807.92:

   f. Provide a separate 510(k) Summary that clearly states"510(k) Summary" on the top of the first page;

   g. Update the Indication for Use shown to be identical to that requested in Deficiency No. 1 above.

   h. Describe in more details on the performance characteristics of the device, , such as how the device functions;

   i. Provide a detailed comparison of the technological characteristics of the subject and predicate devices and justify any differences;

   j. Describe the performance testing conducted on the subject device in greater detail, including electrical testing, biocompatibility testing, bench testing, and clinical validation testing.

   Please note that we may request additional changes to your 510(k) Summary as we continue our review of your file.

Device Description

3. You did not provide sufficient information on device materials. Please provide a table summarizing each component used in the device, including the materials, the additives used (e.g., colorant) and their final concentrations (w/w), and the function of each component. In addition, please provide detailed information on each component (e.g., product name, CAS number, supplier, catalog number, Certificate of Analysis, Material Safety Data Sheet, etc.).

4. You indicated that the personal sensor is colored with a series of color masterbatches. Please work with the supplier to provide the following additional information:

   a. Purity level of colorant

   b. Estimated absolute amount of colorant (in weight) per device

c. Identification of other US legally marketed medical devices by device name, manufacturer, submission number, where the colorants have been previously used, if known

d. Toxicity risk assessment of this colorant that is preferably (b)(4)

e. (b)(4) (if known)

5. Your device description indicates that both the personal sensor and the reader have rechargeable batteries. Please provide more information on both sets of batteries (type, rated voltage, and capacity in mAH). Please clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just the batteries in the reader.

6. Please identify how the batteries are accessed. Explain how you keep the user from accessing the batteries.

7. You indicated that the vaginal personal sensor measures and records BBT data and transfer data to the reader via an electromagnetic induction link. It is not clear how the data is processed. You mentioned that BBT data is measured in (b)(4); therefore, multiple data points are collected each night. It appears that the graphs and other data presented to the user include one BBT data point per night. It is not clear how this data point is derived. Please explain how this is done. Further, please provide information on how fertile days are derived from the data.

8. Further, explain whether any data is considered unusable, such as too low, too high, etc. How is this data handled? How are the data calculated when values are unusable or missing?

Software

9. We were unable to locate an adequate description of the software algorithm for OvuSense in your submission. Therefore, it is unclear how the OvuSense software uses the data collected from the Personal Sensor to calculate/estimate the day of ovulation. Other details of the software algorithm are also unclear, such as whether the software adjusts the algorithm as data on multiple cycles from a user accumulates. Please provide a clear description of the OvuSense software and how it uses data on continuous resting nocturnal vaginal temperature measurements to estimate the day of ovulation. Please also explain whether or not data from multiple cycles is used to adjust the estimate of the date of ovulation.

10. Your Hazard analysis indicates compliance of the battery charger with EN 60601-1 for mitigation of Energy Hazards (electric shock, burn, fire). However, this only ensures that the charger safely provides the power and/or trickle charge in a safe way; i.e., that the charger is electrically safe. This does not ensure that the entire device is electrically safe. Please revise

your Hazard analysis to reflect all mitigations to address electrical shock, burn, fire, explosion, and battery leakage. Also address both sensor and reader interface with the user.

11. Your document titled "System Acceptance Test & Trace Specification" is identified as fulfilling the requirement for a traceability analysis/matrix document. This document includes a table that provide a requirement identification number (format xxx_xxx_###) and identification of the corresponding test number (format test##). However, this document does not include any reference to hazards. Further, the hazard analysis does not appear to include reference to requirements or software tests. The reference number included in the hazard analysis chart uses a format (x.x) that does not correspond to any numbers we can identify. Also, no test ID numbers are included. Thus, the hazards are not tied to tests in the hazard analysis or the traceability analysis.

    While we understand that not all hazards will have a correlating software test, the functional failure hazards should include some software testing (specifically identified). All or most of the hazards should have a correlation to the requirements. Please explain where this is provided in the documentation we have or provide an additional document that shows correspondence between all of the following: requirements, testing, and hazards.

12. Your software revision level history only indicates that the current version is (b)(4) Please identify previous versions (developmental versions) and a brief description of difference with each version

Electricity Safety and Electromagnetic Compatibility Testing

13. General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. Please explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

14. Please explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this related to use with a DC power supply or batteries?

15. The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. Please explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply or to the batteries, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

Material Testing

16. (b)(4) testing was included in your submission to support the biocompatibility of the patient contacting portions of your proposed device. The test methods identified would be supportive of a device with limited contact with mucosal tissues. However, the proposed device will be used daily for up to 21 days per month and

may be used for many months. Therefore, this device could be considered a permanent implant in contact with mucosal tissue. Per FDA Bluebook memo G95-1, testing to support long-term use of the device would include (b)(4) [redacted]

17. You indicated that the personal sensor is colored with a series of color "masterbatches". Please clarify if you plan to market one or multiple color versions of the sensor. If more than one color sensor is proposed, independent biocompatibility testing will be needed to support each color version proposed, unless you can show that the identical materials (supplier, catalog number, colorants, mold release agents, contact potential, etc) have been used in a 510(k)-cleared device. (b)(4) [redacted]

Performance Testing- bench

18. Please provide mechanical testing to assess (b)(4) [redacted].

Performance Testing-Clinical

19. Of the three sections in your submission discussing the clinical validation study (Section 10, Attachment M and Attachment R), none explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined (b)(4) [redacted] (b)(4) [redacted]. The only actual data provided were (b)(4) [redacted]. No other information was provided to support the conclusion that the OvuSense predicted the day of ovulation with greater accuracy compared to the once-daily oral BBT. (b)(4) [redacted]

(b)(4)). In order for FDA to independently verify your conclusion regarding the relative performance of OvuSense vs. oral BBT measurement, please provide all line data for each subject. Also, please provide a statement of your pre-specified statistical hypothesis test and definition of study success. (b)(4)

20. Your study plan as described in Attachment M refers to Freundl *et al.* (2003) and Colombo and Masarotto (2000) as the basis for study methodology for comparing the OvuSense vs. BBT. Freundl *et al's* (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. Please explain why you believe these two references are appropriate as the basis for the study design. Please also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of ovulation as a gold standard to support the proposed Indication for Use.

21. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, you state that the results (b)(4)

22. The OvuSense is the first extended use vaginal probe for basal body temperature measurement. It is important, therefore, that you demonstrate the probe does not cause pain, discomfort, bleeding, etc. In Attachment R, you have stated "No adverse effects were reported" in the clinical validation study. Your submission does not describe, how safety was evaluated in the clinical validation study of the OvuSense. Please explain how safety information was obtained to support their conclusion.

Labeling

23. You have provided the primary and underside labeling for both the OvuSense Sensor and Reader in the submission. Please revise the labels as follows:

    a. Add storage conditions;
    b. Add lot number and expiration date;
    c. The label includes a number of unrecognized symbols; please add text directly next to each symbol on the primary and underside labels for both the OvuSense sensor and reader.
    d. Include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"**to both labels.

24. Please make following changes to the User Manual:

a. Add a separate Device Components Section at the beginning of the User Manual that lists all components of the device;

b. Add a separate Warnings and Precautions Section at the beginning of the User Manual that includes Warnings and Precautions that are currently located throughout the User Manual.

c. Please include the statement **"THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE"** in an individual text box in a prominent location on the front of the User Manual.

d. Add a separate Direction for Use Section that instructs the user explicitly, step-by-step, how to operate the device that is currently located throughout the User Manual.

e. On page 3 of the User Manual, you stated that the user could recycle the used reader and sensor. The sensor is a personal, single user device with a 3 month use-life. The reader does not have an expiration date or use-life. Please state explicitly if the reader is a single user device and how long the use-life is.

f. On pages 6 of the User's Manual you stated that "If you do not have a regular cycle length, OvuSense may still provide you with information about your menstrual cycle and timing of ovulation." Please provide data to substantiate this claim, or remove this claim from device labeling.

g. The personal sensor is an intra-vaginal, tampon-shaped device. On Page 13, you mentioned there may be a small risk of toxic shock syndrome, a rare condition caused by the growth of *Staphylococcus aureus* on blood or fluids in the vagina. Because the user may not be familiar with this medical emergency, please provide detailed explanation of the disease and include all warning signs. Please consider using the information from 21 CFR 801.430 (d), which is the regulation for menstrual tampon labeling.

h. On Page 25, you stated that "the OvuSense Scales graphs using relative temperature points for each cycle". Please clarify what this means and how relative temperature points are related to the BBT.

i. On Page 33, you stated that "if you experience… discomfort, irritation, or a vaginal discharge during use of the personal sensor, stop using to the personal sensor immediately and consult your doctor". This statement seems to be contradicted to your statement of "No adverse effects were reported" in the clinical validation study. Please clarify the discrepancy.

j. The label includes a number of unrecognized symbols; please add text directly next to each symbol used in the labels.

Please note that we may identify additional labeling deficiencies following review of your updated labeling and your responses to the questions in this additional information letter.

Administrative Requirements

25. Please provide Standards Data Report for 510(k) Forms (Form 3654) for all the standards you referenced to complete the performance testing requested in this review memo. You can access this from using the following link: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM081667.pdf.

26. Your 510(k) did not include the Certification of Compliance with Requirements of the ClinicalTrials.gov Data Bank (Form 3674). Effective December 26, 2007, all firms submitting a
5 10(k) are required to submit Form 3674 regarding registration of applicable clinical trials in the Clinical Trials Data Bank (http://prsinfo.clinicaltrial.gov). Form 3674 can be obtained by going to the following web address:
http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf. Please submit Form 3674 for review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum

Date: September 12, 2012

From: Kathryn S. Daws-Kopp
Electrical Engineer

Subject: K122337
Fertility Focus
OvuSense Advanced Fertility Monitoring System

To: Michelle Luo

As requested, this review is intended to address software and electrical safety.

Indications

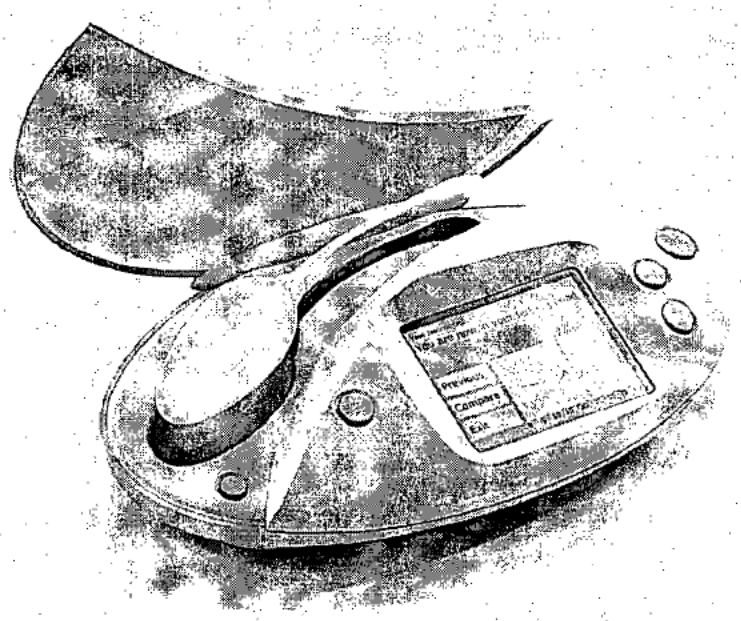
"The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception)."

Device Description

The Fertility Focus OvuSense Advanced Fertility Monitoring System is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating.

The OvuSense device consists of the following components:

- Personal Sensor: Cleaned and then inserted into the vagina and left in place overnight for up to 12 hours, to record basal body temperature. The device is removed in the morning, cleaned and placed on the cradle where the data is downloaded via electromagnetic induction.
- Reader: Stores body temperature data from the Personal Sensor, and provides a storage place for the Personal Sensor during the day when not in use. Reader is battery operated and has a back up a/c power plug.
- User Interface: Consists of an LCD display, five buttons, and software menu-driven screens which allow the user to interact with the Reader and view status information.
- Software: Application software which calculates and displays data, as well



The personal sensor has a microcontroller, RF communications circuitry, and an internal battery. It has a life of less than 6 months; replacement after 3 months is recommended. The sensor is responsible for monitoring and recording temperatures (b)(4) during each night long (12 hours maximum) session. Data is downloaded from the sensor when it is placed, in the proper orientation, in the reader. The download is accomplished by an electromagnetic induction link. The reader accumulates the data, process the data, takes commands from the user (via buttons), and displays data (scale graphs and cycle information). Some information (first day of menstrual period) is input by the user via the buttons. The reader also has rechargeable batteries.

Review Summary

Electrical Safety

They identify that testing has been conducted to the following standards:

BS EN60601-1-4:2000	Medical electrical equipment. General requirements for safety Collateral standard. General requirements for electrical programmable medical systems.
IEC60601-1:2006	Medical equipment. Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Report No: TRA-004397-34-02A

Reports are provided in Attachment O. General safety testing was conducted by a third party, (b)(4). Testing refers to the input as 3 Vdc, but also identifies a PSU (power supply unit), which is presumably the charger unit. The PSU is identified in the notes as being a 9 Vdc power supply. Testing also occurs at 90 and 246 Vac and 50 and 60 Hz. I am, in general, more concerned about the safety of the reader than the sensor.

Hazard analysis states that the Mains charger is compliant with EN60601-1. This addresses the safety of the charger alone and not the safety of their device.

Issues:

Your device description indicates that both the sensor and the reader have rechargeable batteries. Please provide more information on both sets of batteries (type, rated voltage, and capacity in mAH). Please clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just the batteries in the reader.

Please identify how the batteries are accessed. Explain how you keep the user from accessing the batteries.

General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. Please explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

Please explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this related to use with a DC power supply or batteries?

The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. Please explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply or to the batteries, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

Electromagnetic Compatibility (EMC)

They identify that testing has been conducted to the following standards:

EN60601-1-2:2007	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests Report No: TES 004397-01
EN301 489-3 v1.4.1	Electromagnetic Compatibility and Radio Spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3: Specific Conditions for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz Report No: TES 004397-01
EN302 291 v1.1.1	Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Close Range Inductive Data Communication equipment operating at 13,56 MHz; Part 2: Harmonized EN under article 3.2 of the R&TTE Directive. Report No: TES-004397WEU1

I am not sure how radio testing is applicable, although they appear to be EMC related. The referenced standards for this are not ones I am familiar with and they are not recognized by FDA.

Electromagnetic compatibility testing was conducted by a third party, (b)(4) [redacted]. This testing included the following (these documents are European versions of the CISPR and IEC documents we normally see):

Emissions

EN550022:2006 +A1:2007	Radiated and conducted, Class B
EN61000-3-2:2006+A2:2009	Harmonic Emissions
EN61000-3-3:2008	Voltage fluctuations, flicker emissions
Immunity	
EN61000-4-2:2009	Electrostatic discharge
EN61000-4-3:2006+A2:2010	Radiated RF
EN61000-4-4:2004+A1:2010	Electrical fast transient/burst
EN61000-4-5:2006	Surge
EN61000-4-6:2009	Conducted RF
EN61000-4-8:2010	Power frequency (50/60Hz) magnetic field
IEC61000-4-11:2004	Voltage dips, short interruptions and voltage variations on power supply input lines

A quick review of the test report indicates that not all options were tested for each of the tests, but about half were tested and the device appears to have passed the testing as the report concludes. No deviations appear to have occurred. The company did not appear to request any changes in the nature of the pass/fail criteria. I glanced at the radio testing and the device appears to be compliant. I am not familiar enough with the topic to be able to judge, but it appears to cover other aspects of EMC from the EN/IEC testing we normally see. In general, this testing appears to sufficiently address EMC.

Software

As noted in software description, the software language is (b)(4) and runs on a (b)(4). The software controls the user interface, interfaces between sensor and reader, and processes the data collected by the sensor.

It is not clear how the data is processed. Although multiple data points are collected each night, it appears that the graphs presented to the user include 1 data point per night. It is not clear how this data point is derived. An algorithm is mentioned, but it is not included in the software documentation and does not appear to be discussed in the labeling or device description.

Issue:

It is not clear how the data is processed. Although multiple data points are collected each night, it appears that the graphs and other data presented to the user include 1 data point per night. It is not clear how this data point is derived. Please explain how this data point is derived. Further, please provide information on how fertile days are derived from the data.

Further, explain whether any data is considered unusable, such as too low, too high, etc. How is this data handled? How is data calculated when values are unusable or missing?

Version: Version 1.3		
Level of Concern: They identify the level of concern as minor and we agree		
	Yes	**No**
Software description: Section 5.2	✓	
Device Hazard Analysis: Section 5.3	✓	
Software Requirements Specifications (Summary only): Section 5.4	✓	
Architecture Design Chart: not required for minor	NA	
Design Specifications: not required for minor	NA	

Traceability Analysis/Matrix: Section 5.5	✓
Development: not required for minor	NA
Verification & Validation Testing: Section 5.6	✓
Revision level history: Section 5.7	✓
Unresolved anomalies: not required for minor	NA

Software description:
The information is provided in Section 5.2.

The information provided indicates that the programming language is (b)(4) and runs on a (b)(4) (b)(4) Amounts/types of memory are also provided,

The software operating environment is covered, but software features are not. However, this is sufficiently covered by Software requirement specification.

This documentation adequately fulfills the requirements for software description.

Device Hazard Analysis:
This information is provided in Section 5.3.

A chart of hazards is provided as well as a discussion of severity, probability and risk. Acceptable risk (in terms of severity and probability) is also defined. The chart includes the following columns: hazard, reference number, root cause, consequence, pre-mitigation (severity, probability, and risk), mitigation, and post-mitigation (severity, probability, and risk). All appropriate issues appear to be included such as *biocompatibility, electrical safety, tears to sensor, etc. Some mitigations may need further* explanation/discussion, but that will be addressed in other sections, such as testing.

The reference number included in the chart uses a format (x.x) that does not correspond to any numbers we can identify (i.e., requirement tag or verification test tag from the traceability analysis) Also, no test ID numbers are included. Thus, the hazards are not tied to tests here or in the traceability analysis. See *question under traceability section.*

> **Your Hazard analysis indicates compliance of the battery charger with EN 60601-1 for mitigation of Energy Hazards (electric shock, burn, fire). However, this only ensures that the charger safely provides the power and/or trickle charge in a safe way; i.e., that the charger is electrically safe. This does not ensure that the entire device is electrically safe. Please revise your Hazard analysis to reflect all mitigations to address electrical shock, burn, fire, explosion, and battery leakage. Also address both sensor and reader interface with the user.**

This documentation does not adequately fulfill the requirements for Device hazard analysis.

Software Requirements Specifications:
The required Summary is provided in Section 5.4.

This summary is provided in the form of a table, which lists the following as requirements of the software (highlights, not inclusive):

- User interface
- Battery monitoring
- Sensor data download
- Data processing (including checks and filtering)

- Calculation BBT
- Generation of fertility information and graphs
- Data storage and retrieval)

This documentation adequately fulfills the requirements for software requirements specification summary.

Architecture Design Chart:
This documentation is not required.

Design Specifications:
This documentation is not required.

Traceability Analysis/Matrix:
Section 5.5 indicates that the traceability is provided in Attachment J.

Section 4 includes a chart that gives: requirement tag, verification test tag, and comment. Test tags correspond to one of the 13 tests indicated in the chart below under testing. This is part of the require d, but there is no tie to hazards or the hazard analysis table. Individual steps in test are not identified—just the general test number.

Your document titled "System Acceptance Test & Trace Specification" is identified as fulfilling the requirement for a traceability analysis/matrix document. This document includes a table that provide a requirement identification number (format xxx_xxx_###) and identification of the corresponding test number (format test##). However, this document does not include any reference to hazards. Further, the hazard analysis does not appear to include reference to requirements or software tests. The reference number included in the hazard analysis chart uses a format (x.x) that does not correspond to any numbers we can identify. Also, no test ID numbers are included. Thus, the hazards are not tied to tests in the hazard analysis or the traceability analysis.

While we understand that not all hazards will have a correlating software test, the functional failure hazards should include some software testing (specifically identified). All or most of the hazards should have a correlation to the requirements. Please explain where this is provided in the documentation we have or provide an additional document that shows correspondence between all of the following: requirements, testing, and hazards.

This documentation does not adequately fulfill the requirements for traceability.

Development:
This documentation is not required.

Verification & Validation Testing:
Section 5.6 indicates that the validation and verification testing is provided in Attachment K. Testing is also summarized (listed) in a table in Section 5.6.

The list in Section 5.6 includes the following:

Table 5.6
OvuSense Software Verification Tests

Verification Test No.	Test Title
Test 1	(b)(4) [redacted]
Test 2	
Test 3	
Test 4	

Test 5	(b)(4) [redacted]
Test 6	
Test 7	
Test 8	
Test 9	
Test 10	
Test 11	
Test 12	
Test 13	

All 13 tests are described. Each test has a section number (x.x.x) and each step (setup and test) has a line number. Some lines have sublines which are given alpha-characters (a, b, etc.) The testing appears to be thorough and the format lends itself to citation down to the individual step.

This documentation adequately fulfills the requirements for verification and validation testing.

Revision level history:
This information is provided in Section 5.7. The release version only is given.

Issue

Your revision level history only indicates that the current version is version 1.3. Please identify previous versions (developmental versions) and a brief description of difference with each version.

This documentation does not adequately fulfill the requirements for revision level history.

Unresolved anomalies:
This documentation is not required.

Questions to company

Device Description

1. It is not clear how the data is processed. Although multiple data points are collected each night, it appears that the graphs and other data presented to the user include 1 data point per night. It is not clear how this data point is derived. Please explain how this data point is derived. Further, please provide information on how fertile days are derived from the data.

   Further, explain whether any data is considered unusable, such as too low, too high, etc. How is this data handled? How is data calculated when values are unusable or missing?

2. Your device description indicates that both the sensor and the reader have rechargeable batteries. Please provide more information on both sets of batteries (type, rated voltage, and capacity in mAH). Please clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just the batteries in the reader.

3. Please identify how the batteries are accessed. Explain how you keep the user from accessing the batteries.

Testing

4. General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. Please explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

5. Please explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this related to use with a DC power supply or batteries?

6. The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. Please explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply **or to the batteries**, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

Software

7. Your Hazard analysis indicates compliance of the battery charger with EN 60601-1 for mitigation of Energy Hazards (electric shock, burn, fire). However, this only ensures that the charger safely provides the power and/or trickle charge in a safe way; i.e., that the charger is electrically safe. This does not ensure that the entire device is electrically safe. Please revise your Hazard analysis to reflect all mitigations to address electrical shock, burn, fire, explosion, and battery leakage. Also address both sensor and reader interface with the user.

8. Your document titled "System Acceptance Test & Trace Specification" is identified as fulfilling the requirement for a traceability analysis/matrix document. This document includes a table that provide a requirement identification number (format xxx_xxx_###) and identification of the corresponding test number (format test##). However, this document does not include any reference to hazards. Further, the hazard analysis does not appear to include reference to requirements or software tests. The reference number included in the hazard analysis chart uses a format (x.x) that does not correspond to any numbers we can identify. Also, no test ID numbers are included. Thus, the hazards are not tied to tests in the hazard analysis or the traceability analysis.

   While we understand that not all hazards will have a correlating software test, the functional failure hazards should include some software testing (specifically identified). All or most of the hazards should have a correlation to the requirements. Please explain where this is provided in the documentation we have or provide an additional document that shows correspondence between all of the following: requirements, testing, and hazards.

9. Your revision level history only indicates that the current version is version 1.3. Please identify previous versions (developmental versions) and a brief description of difference with each version

Review Conclusion:

Provide the deficiencies identified above as part of an AI letter to the company.

Kathryn S. Daws-Kopp 10/1/12

Kathryn S. Daws-Kopp Date

From: Corrado, Julia A
Sent: Thursday, September 13, 2012 3:56 PM
To: Luo, Michelle T
Cc: Blyskun, Elaine
Subject: Clinical review of Fertility Focus OvuSense Advanced Fertility Monitoring System (K122337)

September 13, 2012

Michelle,

I have reviewed the above premarket notification 510(k) submission for a digital vaginal basal body temperature probe and software for predicting ovulation. Here are my comments:

Device Description

The device consists of the following components:

Personal (Vaginal) Sensor

This is a non-sterile tampon-shaped vaginal insert made from (b)(4) It is 4.5 x 1 x 0.4 inch in dimensions. It contains an (b)(4) and (b)(4) . It must be used with an internal battery.

Battery Operated Reader

This is a unit that stores the vaginal sensor when it is not in use. It receives data from the vaginal sensor via an electromagnetic induction link. The Reader is 7 x 4 x 1.25 inch in dimensions. It has an LCD display that informs the user, among other things, her time of maximum fertility. It also displays "scale graphs" of vaginal temperature profile.

User Interface

This is a 2 x 1.5 inch color LCD display, five buttons and software menu-driven screens with which the user interfaces with the Reader.

Software

The device software runs on a (b)(4) . Software inputs include personal sensor data (primarily basal body temperature), battery status data, User Request data and Fault status.

Proposed Indication for Use

The OvuSense is intended for measuring and recording basal body temperature as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Predicate Device

BioSelf 2000 Fertility Indicator (K904211)

The Bioself 2000 Fertility Indicator is an aid in identifying the fertile period of a woman's menstrual cycle in order to achieve conception. The device is not to be used for contraception.

Clinical Performance Data

Section 10.2 of the submission is called "Design Validation Testing - Clinical Investigation." This section is an overview of the results of a clinical validation study to investigate the efficacy of an indwelling

vaginal temperature monitor to identify and predict ovulation. The actual clinical protocol is in Attachment M (pages 1-37). Attachment R is titled "Clinical Investigational Report for the Ovusense Advanced Fertility Monitor Also Known As Advanced Fertility Monitoring System(AFMS)."

This was a prospective, non-randomized, longitudinal, observational, open label study at a single site.

(b)(4)

(b)(4)

Inclusion Criteria

- Age 20-37
- Cycle length 26 - 36 days
- BMI 19 - 29
- Must not have used oral contraception or hormonal treatments, nor have been lactating for two previous cycles
- Must not be taking any regular medication which could alter BBT, cycle or ovulation
- Must pass an inspection for vaginal health (including swab and screen for Chlamydia)
- Signed Informed Consent
- Available for ultrasound scan for up to three consecutive days at around the time of ovulation
- less than three miscarriages

Exclusion Criteria

- Known abnormal ovulation, abnormal cycles
- Age < 20 or >37
- Reported cycle length outside of range of 26-36 days
- Use or oral contraception, hormonal treatments or lactating within two previous cycles
- Taking regular medication which could alter BBT, cycle or ovulation
- Failure at inspection for vaginal health
- abnormal patterns of sleep or shift worker
- three or more miscarriages

Study Hypothesis

There is no clear statement of the study hypothesis in the submission.

From Section 6 of Attachment M, "Statistical Considerations and Sample Size", it appears that the hypothesis is directed at testing the equivalence of the AFMS to the oral temperature measurement method for detecting ovulation. The following is excerpted from this section:

(b)(4)

(b)(4) [redacted]

Refs: **Freundl G, Godehardt E, Kern PA et al. Estimated maximum failure rates of cycle monitors using daily conception probabilities of the menstrual cycle. Hum Reproduction 2003; 18(12): 2628-2633.**

Colombo B and Masarotto G. Daily Fecundability: First results from a new data base. Demographic Research 2000; 3(5):

Section 6 of Attachment M also states:

(b)(4) [redacted]

Study Methodology

Study subjects wear the Personal Sensor during sleeping . They also take an early morning oral BBT measurement beginning on the first day after the cessation of menses and until onset of next menses. Luteinizing Hormone (LH) urine test kits will be used to plan transvaginal ultrasound assessments of follicular development and document collapse of the dominant ovarian follicle. (b)(4) [redacted]

Target enrollment for the study was (b)(4) [redacted] with the goal of collection of data from (b)(4) [redacted].

Results

(b)(4) [redacted]

Attachment R states that the investigator conducted a preliminary analysis of data after (b)(4) [redacted]

The only information related to safety outcomes is the sentence "No adverse effects were reported."

Page 6 of 11 of Attachment R, under Materials and Methods, states: "... The [Clinical Investigation Plan] describes the outcome measure as the difference in time (days) of the day of ovulation estimated by the competing methods, from the day of ovulation estimated by the US gold standard, weighted by the probability of conception for the day (calculated using the gold standard). However, in this analysis the outcome measure that has been used is the unweighted difference in time. This was done as the units are more simply and intuitively interpreted as "days" and additionally a weighting could not be used for the additional analysis of 'agreement' between the methods. Further, it should be noted that weighting would have actually amplified the results as it would provide a negative bias against the method most

consistently distant from the gold standard."

(b)(4) .

(b)(4) .

Section 4.1 of Attachment R summarizes the results of the primary endpoint analysis as follows:

"The mean estimated day of ovulation by AFMS was 1.610 (SE 0.357) days in advance of the US estimate and the mean estimated day of ovulation by OT was a further 1.853 (SE 0.469) in advance of the AFMS estimate ($p<0.001$, 3.463 days in advance total." There is no explanation as to how the estimated day of ovulation was calculated by the AFMS. It appears from references to literature that the day of ovulation determined by the OT method was calculated using the (b)(4)

It is impossible from the information provided to verify the above results.

Clinical Review Issues

1. The sponsor has not explained the software algorithm for OvuSense. It is unclear how the software uses the data collected from the Personal Sensor to calculate the day of ovulation. It is also unclear whether the software adjusts the algorithm as data on multiple cycles from a user accumulates.

2. None of the sections describing the clinical study explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined by the (b)(4) . This is a fundamental information deficit in this submission.

3. The study plan refers to Freundl et al (2003) and Colombo and Masarotto (2000) as the basis for study methodology for comparing the OvuSense vs. BBT. Freundl et al's (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. The sponsor should explain why he believes these two references are appropriate as the basis for the study design. He should also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of ovulation as a gold standard to support the proposed Indication for Use.

4. The discussion of study results in Attachment R did not provide any details of data from study subjects that would allow FDA to independently verify the study conclusions. The only data provided were (b)(4) . No other information was provided to support the conclusion that the OvuSense predicted the day of (b)(4) with greater accuracy compared to the once-daily oral BBT. It is also (b)(4)

5. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, the sponsor states that the results (b)(4) *version of the HMI Requirements Document. This document and the anecdotal feedback was used to produce a final production version of the software (v1.3)."* It is unclear, (b)(4) .

6. The sponsor has not explained how safety was evaluated in the clinical validation study of the OvuSense. The final report merely states "No adverse effects were reported." The sponsor needs to explain how safety information was obtained to support their conclusion.

Recommendation

There are fundamental unanswered questions regarding how OvuSense algorithm calculates/estimates the ovulation date and how the results of the clinical validation study were obtained. There are no safety outcomes data from the validation study to support the sponsor's conclusion that no adverse events occurred. I anticipate, however, that the sponsor will be able to provide information needed to support the substantial equivalence of this device to the Bioself 2000. Please provide the following deficiencies to the sponsor:

1. We were unable to locate an adequate description of the software algorithm for OvuSense in your submission. Therefore, it is unclear how the OvuSense software uses the data collected from the Personal Sensor to calculate/estimate the day of ovulation. Other details of the software algorithm are also unclear, such as whether the software adjusts the algorithm as data on multiple cycles from a user accumulates. Please provide a clear description of the OvuSense software and how it uses data on continuous resting nocturnal vaginal temperature measurements to estimate the day of ovulation. Please also explain whether or not data from multiple cycles is used to adjust the estimate of the date of ovulation.

2. Of the three sections in your submission discussing the clinical validation study (Section 10, Attachment M and Attachment R), none explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined by (b)(4) using the (b)(4). This is a fundamental information deficit in this submission. The only actual data provided were (b)(4). No other information was provided to support the conclusion that the OvuSense predicted the day of ovulation with greater accuracy compared to the once-daily oral BBT. It is also concerning (b)(4) In order for FDA to independently verify your conclusion regarding the relative performance of OvuSense vs. oral BBT measurement, please provide all line data for each subject. Also, please provide a statement of your prespecified statistical hypothesis test and definition of study success. (b)(4)

3. Your study plan as described in Attachment M refers to Freundl *et al.* (2003) and Colombo and Masarotto (2000) as the basis for study methodology for comparing the OvuSense vs. BBT. Freundl et al's (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. Please explain why you believe these two references are appropriate as the basis for the study design. Please also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of (b)(4) as a gold standard to support the proposed Indication for Use.

4. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, you state that the results (b)(4)

6. The OvuSense is the first extended use vaginal probe for basal body temperature

measurement. It is important, therefore, that you demonstrate the probe does not cause pain, discomfort, bleeding, etc. In Attachment R, you have stated "No adverse effects were reported" in the clinical validation study. Your submission does not describe, how safety was evaluated in the clinical validation study of the *OvuSense*. Please explain how safety information was obtained to support their conclusion.

I have no additional comments.

Thanks,

Julia

Date: August 30, 2012

From: Haijing Hu
CDRH / ODE / DRGUD / OGDB

To: Michelle Luo, Ph.D.
CDRH / ODE / DRGUD / OGDB

Subject: K122337 Ovusense Advanced Fertility Monitoring System
Fertility Focus Ltd

Scope: Reprocessing

I. Summary

There are four deficiencies in the original submission related to reprocessing and microbiology.

II. Regulatory History

This is the first round of review.

III. Indications for Use

(As stated on the Indication for Use form provided by the company):
The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

IV. Device Description

The OvuSense advanced fertility monitoring system is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating.

The device contains two physical components (please see the diagram below):

- Personal sensor: The user cleans the sensor and then inserts it into the vagina. The sensor is left in the vagina overnight for up to 12 hours to record basal body temperature. The user removes the sensor in the morning for cleaning, and places it on the cradle where that data is downloaded.

- Reader: The reader stores body temperature data from the personal sensor and provides a storage place for the personal sensor during the day when not in use. The reader does not have direct contact with the user. The reader has a LCD display and buttons so the user can interact with the reader and view status information.

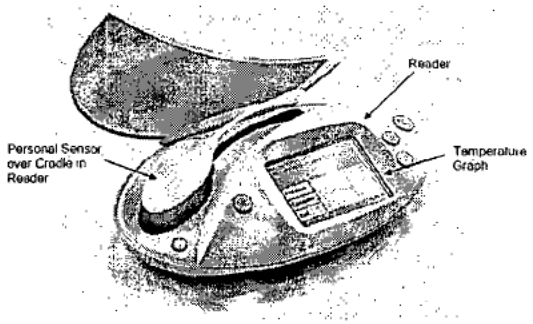


FIGURE 4.1-1: OvuSense Fertility Monitoring System

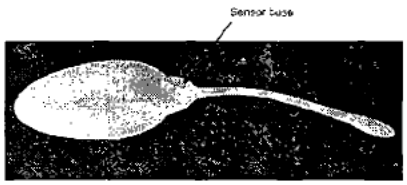


FIGURE 4.1-3: Personal Sensor Showing Base

The system uses the collected data to determine the presence or absence of ovulation and to predict the fertile period for the next menstrual cycle.

The personal sensor is an intra-vaginal device shaped like a small tampon. The sensor is supplied as non-sterile, in a sealed Tyvek pouch. One personal sensor is included in the Ovusense starter pack. The user can purchase the sensors separately. (b)(4) [redacted] A message on the LCD screen of the reader will inform the user when there is only one more cycle of use life left on the sensor. (b)(4) [redacted]. The company stated that the sensor has a shelf life of two years (page 46). This is a single-user, multiple-use device component. The company provided cleaning validation for the sensor.

The reader does not have an expiration date (page 46). It appears to be a single user component. The cradle on the reader has indirect patient contact. It may cause potential infection issues if the personal sensor is not thoroughly cleaned between uses.

V. Cleaning validation

Personal sensor

The company stated in the label that the sensor was a single user device, sharing the sensor might lead to diseases and invalidated the personal data.

The company recommended that the user thoroughly clean the sensor before and after each use and store it in the cradle on the reader when not in use.

The cleaning instruction in the user manual (page 434) includes the following steps:

- Fill the sink with hand-hot water
- Rub a little hand soap on the sensor with fingers
- Dip the sensor in the water and rub thoroughly for 2 minutes
- Rinse all parts of the sensor with tap water to remove any soap residue
- Dry the sensor on a clean towel or tissue

A bioburden report and a cleaning validation report were included in the submission. (b)(4) [redacted]

(b)(4)

[redacted]

FDA does not accept bioburden as a marker for cleaning validation. OGDB does not require strict cleaning validation for certain single user vaginal devices. Therefore, we will not require the company to re-conduct the cleaning validation with another marker. The company will be notified that FDA does not accept bioburden as a sole marker for cleaning validation.

In the user manual the company included toxic shock syndrome (TSS) as one of the precautions for using the device. They recommended that the user stop using the device and see a doctor if she feels ill or have a high temperature. The warning is not sufficient for a lay user who is not familiar with the TSS. The company should provide more detailed explanation of the disease and all related symptoms.

Reader

The reader is not a patient contact component. In the user manual, the company recommended the user to keep the reader clean and wipe the surface, particularly the sensor cradle, with clean paper tissue only. The company stated that disinfection and antibacterial wipes could leave residues on the reader cradle and sensor, which might interfere with the function of the device.

The company included recycling information in the user manual. It appears that the reader is a single user device. However, the company should clarify this. If the reader is a single user device, the company should state this in the user manual explicitly. Otherwise, a validated reprocessing procedure should be included in the user manual.

VI. Deficiencies

I recommend the following deficiencies be sent to the company.

1. You provided a cleaning validation test report for the personal sensor. You used bioburden as a marker for the cleaning validation. Please be advised that FDA recommends against the use of bioburden reduction as a sole test method for cleaning effectiveness. Please use a predetermined discrete absolute endpoint for cleaning validation in your future submissions.

2. You stated conformity to ISO 11737-1:1995 for the bioburden testing. Please be advised that the current FDA recognized version is ISO 11737-1:2006 (R) 2011. Please use the current version of the standard in your future submissions.

3. You stated in the user manual that the user could recycle the used reader and sensor. You clearly stated that the sensor was a personal, single user device with (b)(4) The reader does not have an expiration date or use life. It is not clear if the reader is a single user device, or the user can give it to another person after she finishes using it. Please state explicitly in the user manual if the reader is a single user device. If the reader can be used by a second user, please provide cleaning and disinfection procedures in the user manual and validate the processes.

4. The personal sensor is an intra-vaginal device shaped like a small tampon. You stated in the user manual that there may be a small risk of toxic shock syndrome, a rare condition caused by the growth of *Staphylococcus aureus* on blood or fluids in the vagina. The user of your device may not be familiar with this medical emergency. Please provide detailed explanation of the disease and include all warning signs. Please consider using the information from 21 CFR 801.430 (d), which is the regulation for menstrual tampon labeling.

Haijing Hu, Ph.D.
Microbiologist

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

August 03, 2012

FERTILITY FOCUS LTD
C/O REGSOLUTIONS, LLC
717 LAKEGLEN DRIVE
SUWANEE, GEORGIA 30024
ATTN: PENNY NORTHCUTT

510k Number: K122337

Received: 8/2/2012

Product: OVUSENSE

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

Grayson, Giovanna *

From: Microsoft Outlook
To: 'pennynorthcutt@theregsolutions.com'
Sent: Friday, August 03, 2012 7:26 AM
Subject: Relayed: ack letter

Delivery to these recipients or distribution lists is complete, but delivery notification was not sent by the destination:

'pennynorthcutt@theregsolutions.com'

Subject: ack letter

Sent by Microsoft Exchange Server 2007

K122337

OB/ SRGO

fertility focus

July 31, 2012

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA CDRH DMC
AUG 2 2012
Received

RE: Traditional 510(k)
OvuSense Advanced Fertility Monitoring System

APPLICANT	Fertility Focus Ltd Mo Aslam, PhD Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW 044-1494-510272 (phone) mo.aslam@fertility-focus.com (email)
FDA REGISTRATION #	3006799946
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION	Penny Northcutt, RAC, FRAPS, CQA 717 Lakeglen Drive Suwanee, GA 30024 678-428-6978 (phone) 678-513-0937 (fax) pennynorthcutt@theregsolutions.com (email)
DEVICE CLASSIFICATION	Unclassified Device, fertility diagnostic, proceptive
PRODUCT CODE	LHD

Dear Sir or Madam,

Fertility Focus hereby submits this **Traditional 510(k)** to request clearance for a new device, Fertility Focus OvuSense Advanced Fertility Monitoring System. Fertility Focus wishes to introduce into commercial distribution the Fertility Focus OvuSense, which is the topic of this Premarket Notification.

1-17

We believe the Fertility Focus OvuSense is substantially equivalent to other legally marketed ovulation monitors with the same fundamental scientific technology and intended use, in particular to the predicate device, Bioself 2000 (K904211). Comparisons of the technological characteristics of the Fertility Focus OvuSense and the predicate Bioself 2000 are included in Section 7. Section 8 identifies results of functional/performance testing with acceptance criteria applied. Section 5 details software requirements. Section 9 contains electrical testing results and Section 10 includes the results of clinical testing.

Fertility Focus regards information provided in support of this Traditional 510(k) to be confidential and proprietary and afforded such protection under 21CFR 807.95 and other applicable statutes. We understand that the submission to the government of false information is prohibited by 18 U.S.C. 1001 and 21 U.S.C. 331(q). In accordance with the Safe Medical Devices Act of 1990, a 510(k) Summary of Safety and Effectiveness is included in this notification. A Premarket Notification Truthful and Accurate Statement has also been provided in this submission in accordance with 21 CFR 807.87(j).

A copy of the Medical Device User Fee Cover Sheet is provided with this cover letter.

Per the instructions accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm, an electronic copy is being provided with this submission and it is an exact duplicate of the original paper submission.

We trust that this submission will be satisfactory for review. If there are any questions, or if additional information is required, please contact me at 678-428-6978 (phone) or email to pennynorthcutt@theregsolutions.com.

Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

Form Approved: OMB No. 0910-511. 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) [redacted] 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) Fertility Focus Ltd Warwick Innovation Centre Warwick Technology Park Gallows Hill Warwick West Midlands CV34 6UW GB 1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)	2. CONTACT NAME Mo Aslam 2.1 E-MAIL ADDRESS mo.aslam@fertility-focus.com 2.2 TELEPHONE NUMBER (include Area code) 44-7956862353 2.3 FACSIMILE (FAX) NUMBER (Include Area code)

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

(b)(4) [redacted] 23-Jul-2012

Form FDA 3601 (01/2007)

"Close Window" Print Cover sheet

TRADITIONAL 510(K)
FERTILITY FOCUS OVUSENSE
ADVANCED FERTILITY MONITORING SYSTEM (AFMS)

APPLICANT

Fertility Focus Ltd
Mo Aslam, PhD
Unit 19D, University of Warwick Science Park
Warwick Technology Park, Gallows Hill
Warwick, United Kingdom CV34 6UW
044-1494-510272 (phone)
email: mo.aslam@fertility-focus.com

OFFICIAL CORRESPONDENT FOR THIS SUBMISSION

Penny Northcutt, RAC, FRAPS, CQA
REGSolutions, LLC
717 Lakeglen Drive
Suwanee, GA 30024
Tel: 678-428-6978
Fax: 678-513-0937
email: pennynorthcutt@theregsolutions.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 9010-0120
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)
July 31, 2012	MD6062980-956733	

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)*		
Fertility Focus Ltd	3006799946		
Division Name *(if applicable)*	Phone Number *(including area code)*		
	044-1494-510272		
Street Address	FAX Number *(including area code)*		
Unite 19D, University of Warwick Science Park Warwick Innovation Center, Warwick Technology Park			
City	State / Province	ZIP/Postal Code	Country
Gallows Hill	Warwick	CV34 6UW	United Kingdom
Contact Name			
Mo Aslam, PhD			
Contact Title	Contact E-mail Address		
Technical Director	mo.aslam@fertility-focus.com		

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

REGSolutions, LLC			
Division Name *(if applicable)*	Phone Number *(including area code)*		
	(678) 428-6978		
Street Address	FAX Number *(including area code)*		
717 Lakeglen Drive	(678) 513-0937		
City	State / Province	ZIP/Postal Code	Country
Suwanee	Georgia	30024	USA
Contact Name			
Penny Northcutt			
Contact Title	Contact E-mail Address		
President/CEO	pennynorthcutt@theregsolutions.com		

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

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

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

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

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

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

- ☐ Response to FDA correspondence:

- ☐ 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

- ☐ Repose 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)*:

FORM FDA 3514 (12/10) **PAGE 2 OF 5 PAGES**

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

Product codes of devices to which substantial equivalence is claimed

Summary of, or statement concerning, safety and effectiveness information

☒ 510 (k) summary attached

☐ 510 (k) statement

1	LHD	2		3		4		11 55
5		6		7		8		

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

	510(k) Number	*Trade or Proprietary or Model Name*	*Manufacturer*
1	K904211	Bioself 2000 Fertility Indicator	Bioself, Inc
2			
3			
4			

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification

Device, fertility diagnostic, proceptive

	Trade or Proprietary or Model Name for This Device	Model Number
1	OvuSense	Personal Sensor: M011 Reader: M010 Starter Pack (Personal Sensor and Reader) (Advanced Fertility Monitoring System): M009
2		
3		

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

3	3	3	3	3	3
9	9	9	9	9	9

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
LHD		☐ Class I ☒ Class II ☐ Class III ☐ Unclassified

Classification Panel

Unclassified

Indications *(from labeling)*

The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Note: Submission of this information does not affect the need to submit a 2891 or a 2891a Device Establishment Registration form.	FDA Document Number (if known)

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

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

(b)(4)

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

(b)(4)

☐ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ 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/Postal Code / Country
Contact Name	Contact Title	Contact E-mail Address

FORM FDA 3514 (12/10) **PAGE 4 OF 5 PAGES**

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
ISO 14971	ISO	Application of Risk Management to Medical Devices		2007
IEC 62304	IEC	Medical device software-Software life cycle processes		2006
ISO 10993-10	ISO	Biological evaluation of medical devices – Part 10: Tests for irritation and delayed-type hypersensitivity		2002
ISO 10993-5	ISO	Biological evaluation of medical devices – Part 5: Tests for In Vitro Cytotoxicity		2009
ISO 14155	ISO	Clinical investigation of medical devices for human subjects - Good clinical practice.		2011
BS EN 60601-1-4	EN	Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.		2000
ASTM E1112	ASTM	Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature		2011

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:

Food and Drug Administration
CDRH (HFZ-342)
9200 Corporate Blvd.
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

FORM FDA 3514 (12/10) **PAGE 5 OF 5 PAGES**

Additional Standards

Standards No.	Standards Organization	Standards Title	Version	Date
EN60601-1-2	ISO/EN	Medical Electrical Equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic Compatibility -- Requirements and tests		2001
Standards No.	Standards Organization	Standards Title	Version	Date
IEC60601-1	UL	Medical Electrical Equipment - Part 1: General Requirements for basic safety and essential performance		2006

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 14971:2007 Application of Risk Management to Medical Devices

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#5-40	
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], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[4] The summary report should incluce: 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.

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[6] The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

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STANDARD TITLE [1]

IEC 62304:2006 Medical device software-Software life cycle processes

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#13-8	
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.	☒	☐
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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: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidanc

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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STANDARD TITLE [1]

ISO 10993-10:2002 Biological evaluation of medical devices -- Part 10: Tests for irritation and delayed-type hypersensitivity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-87	
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.	☒	☐
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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: ISO 10993-12:2007 Biological evaluation of Medical Devices - Part 12: Sample preparation and reference

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

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STANDARD TITLE [1]

ISO 10993-5:2009 Biological evaluation of medical devices -- Part 5: Tests for In Vitro cytotoxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-153	
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.	☒	☐
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If yes, was the guidance document followed in preparation of this 510k?	☒	☐

Title of guidance: ISO 10993-12:2007: Biological Evaluation of Medical Devices -- Part 12: Sample preparation and reference

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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STANDARD TITLE [1]

ISO 14155:2011 Clinical investigation of medical devices for human subjects-Good clinical practice

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-181	
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.	☒	☐
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STANDARD TITLE [1]

EN 60601-1-4:2000 Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for el

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)?	☐	☒
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If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) [5] ?	☐	☐
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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: Guidance for Industry and FDA Staff - Guidance for the Content of Pre-market Submissions for Software

[1] *The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]*

[2] Authority [21 U.S.C. 360d]. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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STANDARD TITLE [1]

ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#6-177	
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?	☒	☐
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Were there any deviations or adaptations made in the use of the standard?	☒	☐
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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: Guidance on the Content of Premarket Notification [510(k)] Submissions for Clinical Electronic Thermo

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

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EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

STANDARD TITLE
ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
4.4	Resolution	☒ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *
Deviation to adapt the standard to the device

DESCRIPTION
There is no analog display and there are no Celsius or Fahrenheit gradations.

JUSTIFICATION
Temperature display in OvuSense is graphical display showing relative temperature within each menstrual cycle.

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ Yes ☐ No ☐ N/A

TYPE OF DEVIATION OR OPTION SELECTED *

DESCRIPTION

JUSTIFICATION

SECTION NUMBER	SECTION TITLE	CONFORMANCE?
		☐ 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.

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STANDARD TITLE [1]

IEC 60601-1:2006 Medical Electrical Equipment-Part 1: General Requirements for basic safety and essential performance

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)?	☒	☐
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STANDARD TITLE [1]

EN 60601-1-2:2001 Medical Electrical Equipment-Part 1-2: General requirements for basic safety and essential performance-Collat

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☐	☒
FDA Recognition number [3] #		
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[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 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

510(K) PREMARKET NOTIFICATION
OVUSENSE ADVANCED FERTILITY MONITORING SYSTEM
FERTILITY FOCUS LTD.

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1. IDENTIFICATION

1.1 APPLICANT, DEVICE MANUFACTURER & DEVICE DISTRIBUTOR

Pursuant to Section 510(k) of the Food, Drug and Cosmetic Act and Part 807, Title 21 of the Code of Federal Regulations, Fertility Focus submits the following information as part of this Traditional 510(k) for the OMNI Sterile Tube Welder.

APPLICANT	Fertility Focus Ltd. Mo Aslam, PhD Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW Tel: 044-1494-510272 Email: mo.aslam@fertility-focus.com
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION	Penny Northcutt, RAC, FRAPS, CQA REGSolutions, LLC 717 Lakeglen Drive Suwanee, GA 30024 Tel: 678-428-6978 Fax: 678-513-0937 Email: pennynorthcutt@theregsolutions.com
FERTILITY FOCUS ESTABLISHMENT REGISTRATION NO.:	3006799946 Fertility Focus is a Specification Developer who uses Contract Manufacturers to make their device
CONTRACT MANUFACTURER:	(b)(4) [redacted]

1. IDENTIFICATION

1.2 DEVICE NAME & CLASSIFICATION

TRADE NAME:	OvuSense Advanced Fertility Monitoring System
COMMON NAME:	Device, Fertility Diagnostic, Proceptive
DEVICE CLASSIFICATION:	Unclassified
PRODUCT CODE:	LHD

1.3 PREDICATE DEVICE INFORMATION

PREDICATE DEVICE:	Bioself 2000 Fertility Indicator, K904211

Indications for Use

510(k) Number (if known):

Device Name: **OvuSense Advanced Fertility Monitoring System**

Indications For Use:

The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ AND/OR Over-The-Counter Use __X___

(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)

3.1 CLINICAL NEED

Ovulation

Ovulation, the release of an oocyte from an ovary of a female animal, is an important step of female reproductive biology because it is required in order that the oocyte may be fertilized by male sperm. In human females, ovulation takes place on approximately day 14 of a typical 28 day menstrual cycle. However, only approximately 10% of women regularly ovulate on day 14 of a 28 day cycle. (b)(4) [redacted]

In general terms, the ability to detect the presence or absence of ovulation is useful both in the diagnoses of disorders of ovulation and in providing information about likely fertility which can be used to choose suitable timing of sexual intercourse in order to increase the odds of pregnancy resulting in accordance with the wishes of the woman. Furthermore, information about the timing of ovulation may be used to choose suitable timing of fertility treatments such as intra-uterine insemination (IUI), artificial insemination, or removal of ova for in vitro fertilization.

It has been estimated that one in six couples have an unwanted delay in conception.[2] Most of those couples do not have absolute infertility (that is, no chance of conception), but rather, subfertility with a reduced chance of conception because of one or more factors in either or both partners.

As part of the diagnoses of subfertility, one of the key questions which the clinician asks is, "Does the woman ovulate?" In addition to answering the above question, knowing when the woman ovulates is also useful in cases of subfertility because it allows the couple and/or the physician involved in providing fertility advice or treatment to time their sexual intercourse and/or therapeutic intervention so as to maximize the chances of conception.

The Ovulatory Cycle

The cyclic changes in ovarian activity are controlled by the secretion of two hormones by the pituitary gland, follicle stimulating hormone (FSH) and luteinizing hormone (LH) under the control of the hypothalamus. During the second half of a preceding cycle, high levels of oestradiol (oestrogen) and progesterone (progestogen) act via the hypothalamus to suppress FSH and LH production by the pituitary gland. At the end of the preceding cycle, a decrease in production of oestradiol and progesterone by the corpus luteum removes suppression of the hypothalamus and FSH levels start to rise. Once a threshold is met, FSH stimulates a cohort of ovarian antral follicles into growth.

The dominant follicle continues to grow towards ovulation and as it does so, it produces increasing amounts of oestradiol. This leads to a fall in FSH which removes support for non-dominant follicles and increases the dominant follicle's receptivity to LH. The high oestradiol level causes the pituitary gland to release a large surge of LH. This peak of LH triggers the rupture of the follicle and release of the oocyte (ovulation) approximately 37 hours after the beginning of the surge of LH or approximately 17 hours after its peak. It is known that during

---

(b)(4) [redacted]

[2] Taylor, A., ABC of subfertility. BMJ, 2003. 327:434-6.

the LH peak a rise in basal body temperature (BBT) occurs. The detection of that rise is used widely as a surrogate marker for ovulation.[3] [4]

The remains of the ruptured follicle becomes the corpus luteum which produces progesterone and oestrogen, and causes an abrupt change in the characteristics of the cervical mucus so as to make it impenetrable to sperm. A decrease in progesterone and oestrogen towards the end of the cycle causes the bleeding of menstruation.

Detection of Ovulation

The US ASRM Guidelines[5] and UK NICE Guidelines[6] for investigating whether ovulation is likely to take place include checking mid-luteal phase progesterone seven days before expected menses. Other investigations which may be carried out to indicate ovulatory cycles including measuring LH, FSH, and oestradiol concentrations in early follicular phase (days 2 to 6).[7]

Laboratory measurement of hormone levels typically requires the drawing of a blood sample or the use of urine tests. Whilst such tests may be highly suitable for occasional diagnostic testing, they have significant drawbacks if they are to be used frequently for long periods of time as they require a visit to a medical facility for taking or deposit of the relevant sample. Several surrogate markets of ovulation that are more suitable for home use and for sustained monitoring have been identified. The first of these involves the woman checking the consistency of her cervical mucus. The second involves the use of over the counter urine dipsticks to measure hormone levels. Urine tests suffer from poor reliability because urine production rates are subject to unpredictable variations that lead to variations in hormone concentrations in the urine in the bladder. The third involves the woman recording her body temperature. As discussed above, the LH peak, which occurs just before ovulation, is associated with a rise in basal body temperature (BBT). The detection of that rise is used widely as a predictable surrogate marker for ovulation.[8] [9]

Hormone spot tests are only really useful if cycle length, and the timing of ovulation within the cycle, are regular.[10]

Body temperature measurement has been shown to generally outperform both the mucus and the urine hormone approaches in identifying ovulation and the fertile period.[11]

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[3] Davis, M.E., & Fugo., The cause of physiologic basal temperature changes in women. Clin. Endocrinol, 1948. 8:550-63.

[4] Coyne, M.D., Kesick, T.J., Circadian rhythm changes in core temperature over the menstrual cycle: Method for non-invasive monitoring. Am J Physiol Regul Integr Comp Physiol, 2000. 279:1316-20.

[5] www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Committee_Opinions/optimal_evaluation_of_the_infertile_female(1).pdf

[6] www.nice.org.uk/guidance/index.jsp?action=byID&o=10936

[7] Taylor 2003

[8] Davis 1948

[9] Coyne 2000

[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC2505167/

[11] Freundl, G., Godehardt, E., Estimated maximum failure rates of cycle monitors using daily conception probabilities in the menstrual cycle. Human Reproduction, 2003. 18:2628-33.

3.2 FERTILITY FOCUS OVUSENSE ADVANCED FERTILITY MONITOR BACKGROUND

Fertility is controlled by many factors, including the vitality of the egg and of the sperm, the timing of the joining of sperm and the egg, the environment of the uterus and fallopian tubes, and by hormonal and biochemical factors. For those women who are trying to achieve pregnancy, they need to understand their ovulation cycle—when it occurs, and most importantly, when her next fertile period will take place.

(b)(4)

[redacted]

See **Attachment A** for literature references.

Purpose of this Submission

The purpose of this 510(k) is to request clearance for a new ovulation monitor and demonstrate substantial equivalence of the Fertility Focus OvuSense to the predicate device, Bioself 2000 Fertility Indicator (K904211).

The differences in design between the OvuSense and the predicate devices are:

- Both the Fertility Focus OvuSense device and the Bioself 2000 measure basal body temperature (BBT). However, the OvuSense takes BBT readings only from the vagina, whereas the Bioself 2000 takes BBT readings from vagina, the mouth, or anus.
- OvuSense takes continuous BBT readings overnight, while the woman is sleeping. The Bioself 2000 user must insert the device upon waking for her BBT reading, within a specific timeframe as tracked by the device.
- OvuSense displays a scale graph of the temperature cycle, while the Bioself 2000 displays the BBT temperature as readings to the user.

4. DEVICE DESCRIPTION

4.1 DEVICE DESCRIPTION

The Fertility Focus OvuSense Advanced Fertility Monitoring System is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating., OvuSense applies an algorithm to this collected data to accurately determine when ovulation occurred in each cycle, or if it was absent, and how long the cycle lasted. The algorithm then uses the determined date of ovulation, matched to the length of cycle, and using this data predicts the window of optimum fertility for the next monthly cycle.

Contra-Indications: Not to be used during menstruation. OvuSense is not designed to be used as a contraceptive device. OvuSense is not designed to be used as a method for detecting or confirming pregnancy. Use of the contraceptive pill, any other hormonal contraceptive, or intra-uterine devices at the same time as use of OvuSense will invalidate the data collected.

The OvuSense device consists of the following components:

- Personal Sensor: Cleaned and then inserted into the vagina and left in place overnight for up to 12 hours, to record basal body temperature. The device is removed in the morning, cleaned and placed on the cradle where the data is downloaded via electromagnetic induction, a closed looped wireless RF by press of a button. A single Personal Sensor is (b)(4) [redacted], and is then replaced by a new one. Supplied non-sterile, in a sealed Tyvek pouch.
- Reader: Stores body temperature data from the Personal Sensor, and provides a storage place for the Personal Sensor during the day when not in use. No direct patient contact. Reader is battery operated and has a back up a/c power plug.
- User Interface: Consists of an LCD display, five buttons, and software menu-driven screens which allow the user to interact with the Reader and view status information.
- Software: Application software which displays user-interface menu screens on the LCD display of the Reader.

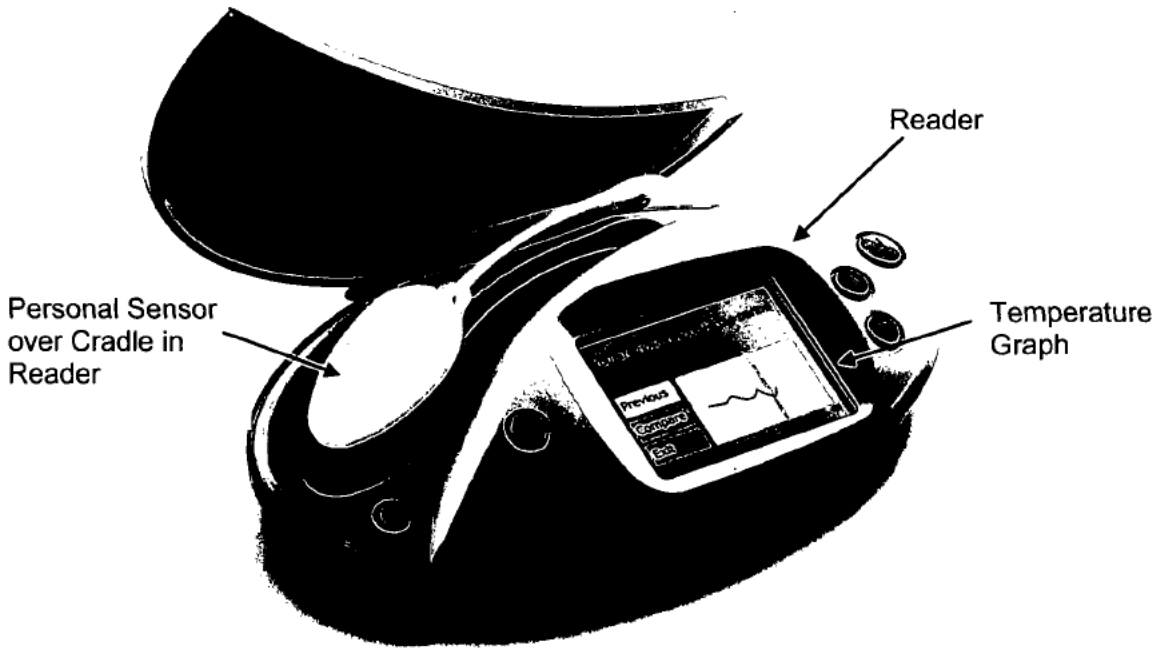


FIGURE 4.1-1: OvuSense Fertility Monitoring System

In the evening, the user cleans the Personal Sensor with soap and water and then inserts it into her vagina before she goes to bed, leaving it in place overnight during sleep. The Sensor is removed in the morning, cleaned with soap and water, and placed on the OvuSense Reader cradle, where the data is downloaded via an electromagnetic induction link. The process is repeated every night of the cycle, excluding times when menstruating. The woman can remove the Personal Sensor to use the bathroom or to have sexual intercourse. She then cleans the Sensor and re-inserts it into her vagina. (b)(4)

Personal Sensor– An intra-vaginal device shaped like a small tampon. It is a surface contacting (mucosal membrane) device. The Personal Sensor is approximately 4.5" x 1" x 0.4" in dimensions. The Personal Sensor is stored in a recessed area on the Reader, known as the cradle, when not in use. When in use, the Personal Sensor is cleaned with soap and water, and then inserted into the vagina before the woman goes to bed, and is left in place overnight for up to 12 hours. The device is removed in the morning, cleaned with soap and water, and placed on the cradle, where the data is downloaded. Data is downloaded from the Personal Sensor to the Reader via an electromagnetic induction link. The Sensor sends the data it has collected to the Reader when it is placed in the cradle on the Reader, with the base of the Sensor neatly aligned, and after the download button on the Reader is pressed.

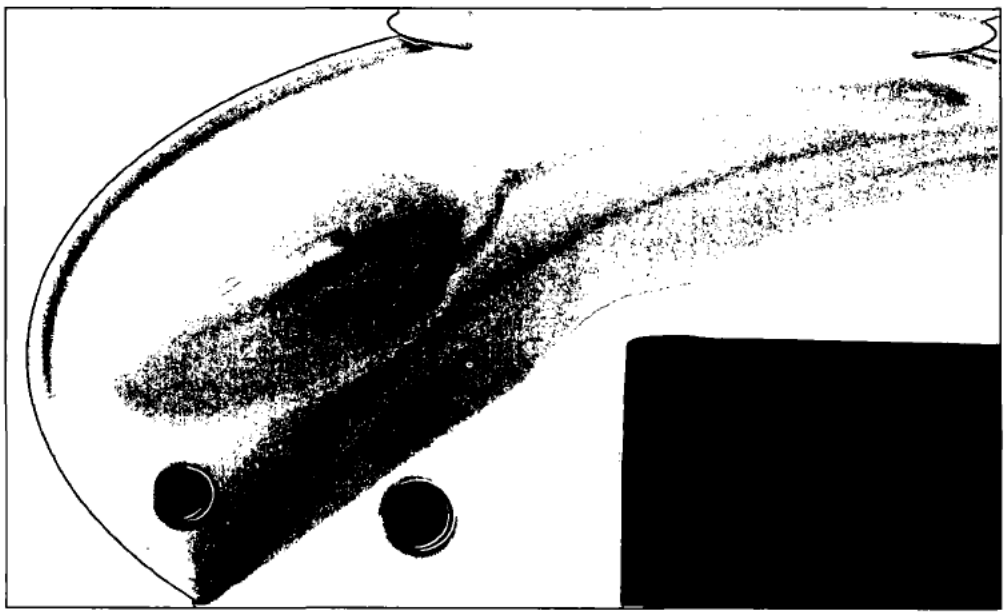


FIGURE 4.1-2: OvuSense Reader Showing Cradle

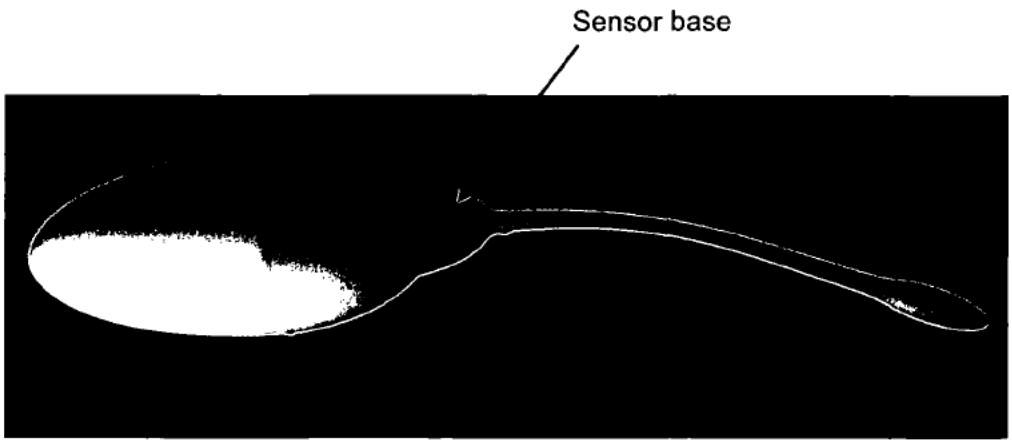


FIGURE 4.1-3: Personal Sensor Showing Base

The Personal Sensor primarily consists of an (b)(4) and RF communications circuitry. The Personal Sensor has an internal battery with life >6 months and is to be used (b)(4). The Sensor is a secondary (slave) device and is responsible for monitoring and recording basal body temperatures every five minutes throughout the night and logging the temperatures in memory.

The Personal Sensor is formed by injection molding as two halves of the shell from liquid silicone rubber which are subsequently joined and sealed using a room temperature vulcanizing (RTV) sealant. Both the main body and the RTV are white in color using the same color master batch.

One Personal Sensor is included in the OvuSense starter pack. Personal Sensors can also be purchased separately. Each Personal Sensor has (b)(4). After a woman uses the Personal Sensor (b)(4), a message displays on the LCD screen of the Reader to let her know that she can only use the Personal Sensor for one more cycle. (b)(4)

(b)(4) [redacted]. The Personal Sensors are supplied clean but not sterile, in a Tyvek pouch.

The Personal Sensor has a temperature measuring range 35.5-42.0° C.

Reader – The unit which stores the Personal Sensor when not in use, and which records and provides information on an LCD display. The Reader has no direct user contact. The Reader is approximately 7" x 4" x 1.25" in size.

The reader accumulates data for each cycle that a woman uses the Personal Sensor. The Reader continues to accumulate data when a new Personal Sensor is used. The reader provides the user with information on her menstrual cycle and also indicates the time of maximum fertility, via messages shown on an LCD display. The Reader displays scale graphs using relative temperature points for each cycle. The Reader displays cycle information for the last three recorded cycles.

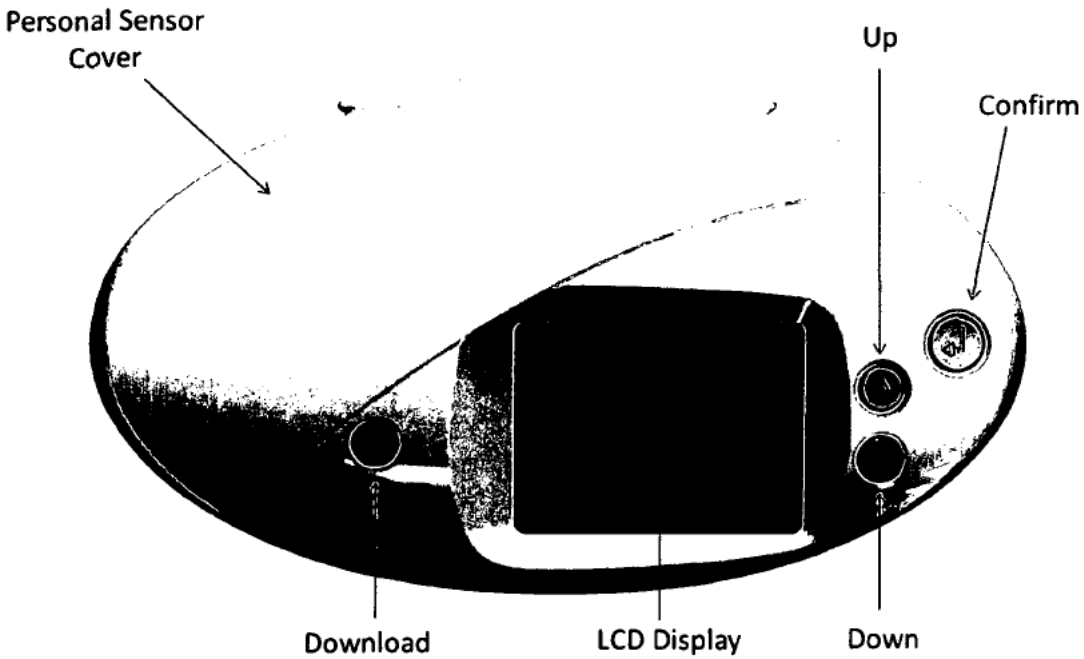


FIGURE 4.1-4: OvuSense Reader

The Reader contains a rechargeable battery. The Reader does not lose information already stored if the main battery becomes flat, but it is not able to download new measurements from the Personal Sensor until the battery is recharged via an A/C adaptor provided with the unit. The Reader acts as a master device by establishing communications with the Personal Sensor on detection of the "download" button key press by the user. The subsequent broadcast message (RF signal) sent by the Reader is received by the Personal Sensor when the Sensor is placed on the Reader device. Once communications have been established, the Reader software downloads the Personal Sensor data and stores this in a local datastore (non-volatile memory).

The Reader consists of the following components:

- Mechanical housing that provides an enclosure for all hardware components and a location for placement of the Personal Sensor (cradle)
- 2" x 1.5 " color LCD screen display
- Embedded processor ([redacted])
- Interface/electronic circuitry necessary for data acquisition [redacted] for communications/data transfer with the Personal Sensor)
- Buttons-The user interacts with the Reader via five buttons (which form part of the mechanical housing) and a software menu-driven display. The buttons are: Sensor Record, Download, Select Up, Select Down, and Confirm.
- [redacted]

FIGURE 4.1-5: Block Diagram Illustraing Key Components and Interface Between Reader and Personal Sensor

The Reader has seven modes of operation:

1. Standby (Low Power) Mode: Device LCD back light is OFF and the default user screen is displayed.
2. Power-On/Self-Test (POST) Mode: Device performs initialization and "health" checks immediately following power-on of device.
3. Download Mode: Reader software downloads data from the Personal Sensor (including enabling/disabling communications with Personal Sensor).
4. Idle Mode: Reader displays the main (default) user screen.
5. Setup Mode: Reader software configures the device date and time based on user input.
6. Input Mode: Reader software processes data input by the user.

7. Display Mode: Reader software formats and displays fertility status information.

No servicing or calibration of the Reader is required by the user. Calibration of the Reader device is performed during production.

User Interface – The user interface consists of a 2" x 1.5" color LCD display, five buttons, and software menu-driven screens which allow the user to interact with the Reader and view status information. A number of screens are presented to the user:

- Main (Default) Screen – Displays when the Reader is powered on and when the device is in idle mode. The user accesses a menu from this screen which allows navigation to other user screens.

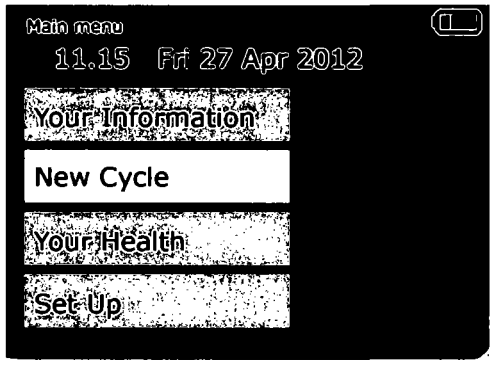


FIGURE 4.1-6: Example Main (Default) Screen

- Setup Screen – Allows the user to set up the device data and time.

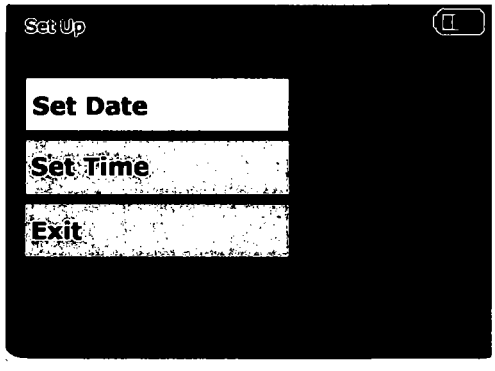


FIGURE 4.1-7: Example Setup Screen

- Data (Input) Screen – Allows the user to enter details of menstruation and days of fever.

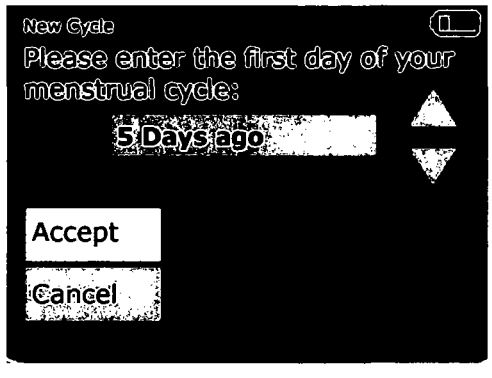


FIGURE 4.1-8: Example Data (Input) Screen

4. DEVICE DESCRIPTION

(b)(4)

Software – Application software, written in C(b)(4), enables user-interface menu screens on the LCD display of the Reader. Software runs on a (b)(4) Electromagnetic induction is used as a communications medium between the Personal Sensor and the Reader device.

Reader software inputs include:

- Personal Sensor Data: Downloaded from the Personal Sensor. Data is primarily basal body temperature, however, in addition, calibration and production data used for identification/tracking of the Personal Sensor is also provided. The Reader software processes the temperature data using a dedicated algorithm to determine fertility status and presents this data on the user interface screens. Data downloaded from the Personal Sensor is stored in non-volatile memory.
- Battery Status Data: Current state of the rechargeable batteries used to power the Reader device.
- User Request Data (button press): Manu navigation commands, request to set date and time, request to input menstruation dates, request to input day of fever, and event markets indicating insertion/removal of Personal Sensor (i.e. start/stop temperature record).
- Fault Status: Detected hardware, software, communication, or user errors.

Reader software outputs include:

(b)(4)

- System Information: Battery status, current date and time, fault status, power status (on/off).

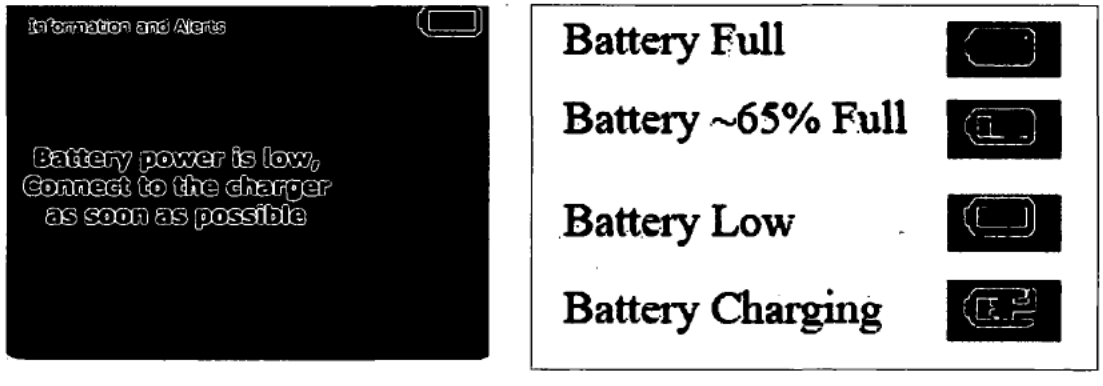


FIGURE 4.1-12: Example of Battery Status Display and Battery Status Indicator Icons

Once the Reader software has completed download and processing of data from the Personal Sensor, the user can view the following information:

(b)(4)

[redacted]

4.2 ENGINEERING DRAWINGS

Engineering drawings, including schematics and PCB layout, for the Fertility Focus OvuSense are provided in **Attachment B**.

4.3 PRODUCT CODE

Product codes for the OvuSense Advanced Fertility Monitoring System are as follows:

TABLE 4.3
OVUSENSE ADVANCED FERTILITY MONITORING SYSTEM PRODUCT CODES

Component	Model Number
Personal Sensor only	M011
Reader only	M010
Starter Pack: Personal Sensor and Reader- Advanced Fertility Monitoring System	M009
Charger Unit	M012-UK, EU, US

4.4 DESCRIPTION OF MATERIALS

The Fertility Focus OvuSense Advanced Fertility Monitoring System components which come into contact with the device user (patient) are made from materials that have been used safely in medical devices for decades. The Reader has indirect contact with the patient. The patient touches the buttons on the Reader to select software-initiated choices. The Personal Sensor has direct contact with the patient during overnight use. The Personal Sensor is made from soft (b)(4) and has no additional coatings or antimicrobial agents.

Materials for the direct contacting component, the Personal Sensor, have been evaluated in accordance with ISO 10993-1 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. A biocompatibility assessment of the materials is included in Section 4.5 of this Submission. See **Attachment C** for OvuSense materials information, including MAF authorizations.

TABLE 4.4
OVUSENSE ADVANCED FERTILITY MONITORING SYSTEM MATERIALS

Component	Materials	Patient Contact
Personal Sensor	(b)(4)	Direct
Epoxy Coating		Direct
Room Temperature Vulcanizing (RTV) Seal		Direct

TABLE 4.4
OVUSENSE ADVANCED FERTILITY MONITORING SYSTEM MATERIALS

Component	Materials	Patient Contact
for Personal Sensor		
Color Master Batch for Personal Sensor	(b)(4)	Direct
Reader Cradle	PC & ABS (b)(4)	Indirect
Reader	PC & ABS (b)(4)	Indirect

4.5 BIOCOMPATIBILITY TESTING

Fertility Focus referred to the ISO 10993-1 guide for selecting appropriate biocompatibility testing. The OvuSense Personal Sensor is considered a surface contacting, mucosal membrane, limited duration device. Biocompatibility tests were performed on final finished OvuSense Personal Sensors. All biocompatibility test results were acceptable.

Biocompatibility studies were conducted by Wuxi-AppTec Laboratories Services, (Registration number 3002199759), and were performed in accordance with Good Laboratory Practices.

TABLE 4.5
OVUSENSE BIOCOMPATIBILITY TESTING

Biocompatibility Test	Result	Attachment
(b)(4)		Attachment D
		Attachment E
		Attachment F
		Attachment G

4.6 PACKAGING INFORMATION

The components used to package the OvuSense Advanced Fertility Monitoring System are all standard packaging materials used in the medical device industry.

TABLE 4.6
OVUSENSE PACKAGING INFORMATION

Design Consideration	Characteristic
1. Packaging Configuration	Configuration 1. Personal Sensor only in double packaging of Tyvek pouch inside of white marketing carton box inside of a shipping carton Configuration 2. Reader only, double-wrapped in bubble wrap inside of white marketing carton box inside of shipping carton Configuration 3. Personal Sensor and Reader-Advanced Fertility Monitoring System together both in pouch inside of a white marketing carton box inside of shipping carton
2. Required Labeling	OvuSense User Manual Serial number included on Reader rear label Serial number for Sensor
3. Packaging Materials	Personal Sensor in Tyvek pouch, shipping carton

Shipping testing for packaging integrity is ongoing per ISTA and will be completed prior to commercial distribution.

4.7 CLEANING VALIDATIONS

Cleaning validations for the OvuSense Fertility Monitoring System were conducted by Wickham Laboratories (Hampshire, England) (FDA registration No. 216813220) to determine bioburden and to validate the cleaning procedure on the OvuSense device during normal use. These validations were performed in accordance with Good Laboratory Practices.

TABLE 4.7
OVUSENSE CLEANING VALIDATIONS

Cleaning Validation	Result	Attachment
(b)(4) [redacted]	[redacted]	Attachment H
[redacted]	[redacted]	Attachment I

Bioburden Validation Protocol

(b)(4) [redacted]

(b)(4)

The test method is described in (b)(4) complies with ISO 11737-1: 1995 (E) Sterilization of medical devices Microbiological methods: Part 1: Estimation of population of microorganisms on products.

Bioburden Validation Report

(b)(4)

Cleaning Validation Protocol

(b)(4)

Bioburden Testing

(b)(4)

[redacted]

Cleaning Validation Report

(b)(4)

[redacted]

4.8 STERILIZATION TESTING

The OvuSense Advanced Fertility Monitoring System is provided clean but not sterile. There is no expiration dating for the Reader but the Personal Sensor has expiry of 2 years .

5. SOFTWARE DOCUMENTATION

5.1 SOFTWARE LEVEL OF CONCERN

The answers to all questions in Tables 1 and 2 of the FDA industry guidance document, Guidance for the content of Premarket Submissions for Software Contained in Medical Devices is NO; therefore, Fertility Focus determined the level of concern to be MINOR.

The software device does not control or contribute to life-sustaining functions. It does not diagnose and it does not provide treatment. The software device will not pose any life threatening injury, cannot inflict permanent impairment of a body function/structure, or require medical or surgical intervention to preclude permanent impairment of a body function/structure to an operator/user as a result of a device failure or design flaw if operated for its intended use.

5.2 SOFTWARE DESCRIPTION

The Reader software runs on a (b)(4). The software is programmed in (b)(4) (b)(4). The interface with the hardware (e.g. driver software for the LCD display) requires sections of the design to be implemented in (b)(4)

(b)(4):

- (b)(4)
-
-

5.3 DEVICE HAZARD ANALYSIS

Table 5.3 that follows provides a tabular description of identified hardware and software hazards for the OvuSense Advanced Fertility Monitoring System, including severity assessment and mitigations.

Severity
A ranking of the seriousness of a hazardous event

Ranking	Severity of Event	Description
C5	Catastrophic	Results in patient death.
C4	Critical	Results in permanent impairment or life-threatening injury.
C3	Serious	Results in injury or impairment requiring professional medical intervention.
C2	Minor	Results in temporary injury or impairment not requiring professional medical intervention.
C1	Negligible	Inconvenience or temporary discomfort.

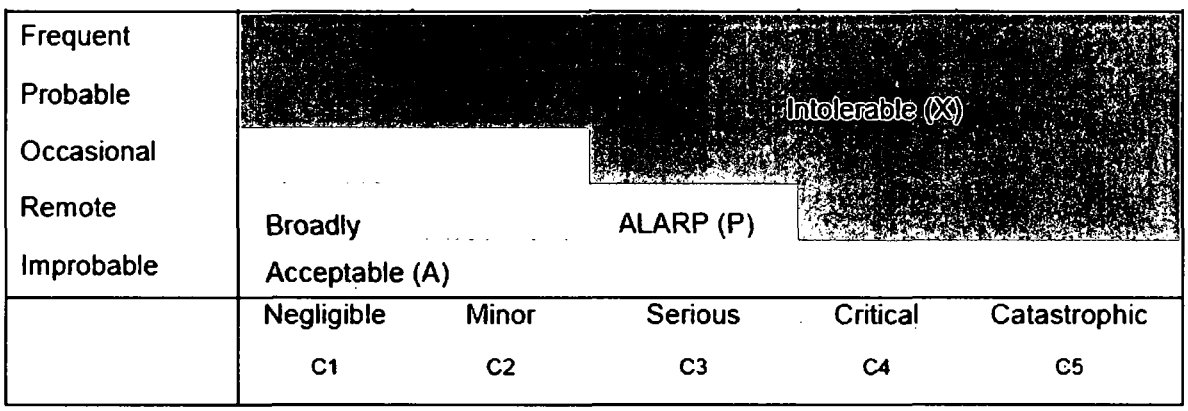
Occurrence

A ranking of the likelihood of occurrence of a hazardous event

Ranking	Probability of Occurrence	Probability
P5	Frequent	$\geq 10^{-3}$
P4	Probable	$< 10^{-3}$ and $\geq 10^{-4}$
P3	Occasional	$< 10^{-4}$ and $\geq 10^{-5}$
P2	Remote	$< 10^{-5}$ and $\geq 10^{-6}$
P1	Improbable	$< 10^{-6}$

Risk Evaluation

The acceptability of risks was assessed and placed into one of three categories:



Acceptable risks are those where the risk is so low compared with the benefit of using the device that no further mitigation was required.

ALARP risks are those that have been reduced to be as low as reasonably practicable. Further reduction would be either technically or economically unfeasible and the benefit to the patient substantially outweighs the risk.

Intolerable risks are those that are too high to be accepted and must be reduced if the device is to be realized.

Table 5.3
Risk Assessment Matrix

(b)(4)

[redacted]

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) Software Verification

(b)(4) CCI [redacted]

5.4 SOFTWARE REQUIREMENTS SPECIFICATION

A summary of functional requirements for the OvuSense Advanced Fertility Monitoring System is provided in Table 5.4.

Table 5.4

(b)(4) CCI [redacted]

5.5 TRACEABILITY ANALYSIS

Traceability among OvuSense Advanced Fertility Monitoring System software requirements, specifications, identified hazards and mitigations, and verification/validation testing is provided in the System Acceptance Test & Trace Specification (SATTS). See **Attachment J**.

The majority of software requirements for the Personal Sensor Reader are verified by demonstration.

Given the length of time it takes to acquire sensor data for the purposes of testing the Reader the most practical testing philosophy is to use predefined data for a number of cycles.

The verification tests first prove that the Reader can acquire data from a Personal Sensor and correctly write this data to its non-volatile memory. Having proved that the non-volatile memory records are correctly created, predefined data is then written to the non-volatile memory to facilitate verification of the ovulation detection and fertility prediction algorithms and data presentation capabilities of the Reader.

5.6 VERIFICATION AND VALIDATION DOCUMENTATION

Software functional test plan, pass/fail criteria, and results for the OvuSense Advanced Fertility Monitoring System are provided in System Acceptance Test Procedures Specification (SATPS). See **Attachment K**.

Table 5.6
OvuSense Software Verification Tests

Verification Test No.	Test Title
Test 1	(b)(4) CCI [redacted]
Test 2	
Test 3	
Test 4	
Test 5	
Test 6	
Test 7	
Test 8	
Test 9	
Test 10	
Test 11	
Test 12	
Test 13	

5.7 REVISION LEVEL HISTORY

The release version of the OvuSense Advanced Fertility Monitoring System software is (b)(4) CCI [redacted]

6. HUMAN FACTORS INTERFACE

6.1 INTENDED DEVICE USERS, USES, USE ENVIRONMENTS AND TRAINING

(b)(4) CCI :

(b)(4) CCI

6.2 HUMAN MACHINE INTERFACE (HMI) REQUIREMENTS

The following table summarizes the Human Machine Interface (HMI) Requirements for the OvuSense Advanced Fertility Monitoring System.

Table 6.2

(b)(4) CCI

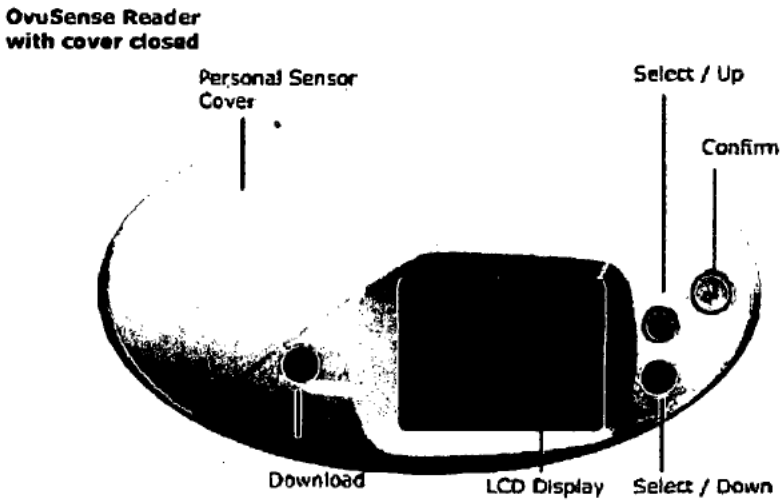
Table 6.2

(b)(4) CCI

[redacted]

6.3 DEVICE USER INTERFACE

The device uses a simple five button interface for user interaction. The Download and Start buttons have specific functions; the up, down, and confirm buttons allow interaction with the software.



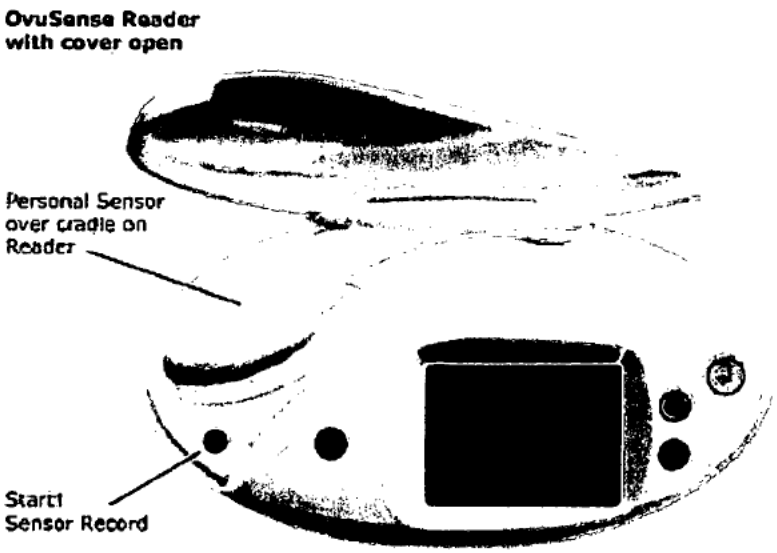


FIGURE 6.3-1: OvuSense User Buttons

The device software is structured on a simple menu system with four main options selectable from the main menu: Your Information, New Cycle, Your Health, and Set Up.

Your Information: (b)(4) CCI [redacted]

6. HUMAN FACTORS INTERFACE

(b)(4) CCI

[redacted]

6.4 SUMMARY OF FORMATIVE EVALUATIONS

The iterative research and development process for OvuSense is described by the following flowchart:

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

6.5 VALIDATION TESTING PHASE 1

A set of (b)(4) CCI (see **Attachment M**), (b)(4) CCI Users were provided with basic training on the unit containing software v1.2, asked to provide anecdotal feedback during their use of the device on the trial and once they had completed their second cycle to complete an anonymised online Usability questionnaire. (b)(4) CCI . The Results derived from this testing were then fed into the software development process via an updated version of the HMI Requirements Document. This document and the anecdotal feedback was used to produce a final production version of the software (v1.3).

(b)(4) CCI

User Manual: The User Manual (see **Attachment L**) has been completely rewritten, and a short guide to daily use brought forward in the manual, but information has all been retained in one place (to avoid potential confusion caused by separate "quick guides" and "reference manual").

(b)(4) CCI

6.6 VALIDATION TESTING PHASE 2

In Phase 2 of validation testing, (b)(4) CCI without reference to new user documentation, followed by (b)(4) CCI on the OvuSense User Manual. As no reference to training materials or user manual was allowed during the response, this is deemed to represent the best experiential test of the final production version of the software (b)(4)

(b)(4) CCI

(b)(4) CCI

[redacted]

6.7 CONCLUSION

OvuSense has been found to be safe and effective for the intended users, its intended uses, and use environments.

(b)(4) CCI

[redacted]

7.1 SUBSTANTIAL EQUIVALENCE DECISION-MAKING PROCESS

The OvuSense Advanced Fertility Monitoring System is substantially equivalent to the Bioself 2000 Fertility Indicator (K904211). Both OvuSense and Bioself have similar intended use/indications for use, principles of operation-basal body temperature reading, technological characteristics-electronic and software driven, and substantially equivalent device designs. Predicate device information is provided in Section 11 of this Premarket Notification. Comparative performance data is provided in Section 8 of this Premarket Notification.

The 510(k) "Substantial Equivalence" Decision-Making Process in ODE Guidance Document #K86-3, *Guidance on the CDRH Premarket Notification Review Program*, was used to determine substantial equivalence. Answers to the relevant questions lead to a determination of substantial equivalence, as follows:

1. DOES THE DEVICE HAVE SAME INDICATION STATEMENTS ..... YES

The FDA cleared Bioself 2000 and the Fertility Focus OvuSense statements are **substantially equivalent**.

The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

The Bioself 2000 Fertility Indicator is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

2. DOES NEW DEVICE HAVE THE SAME TECHNOLOGICAL CHARACTERISTICS, E.G., DESIGN, MATERIALS, ETC.? ..... YES

The Fertility Focus OvuSense was designed to have the same technological characteristics as the predicate Bioself 2000 (K904211). They both measure basal body temperature (BBT) via a vaginal probe and use a software algorithm to predict a woman's ovulation pattern. The Fertility Focus OvuSense utilizes a computer algorithm to predict fertility, as does the Bioself 2000 (K904211) predicate device.

The FDA cleared Bioself 2000 and the Fertility Focus OvuSense technological characteristics are **substantially equivalent**.

3. ARE THE DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH TO ENSURE EQUIVALENCE? .... YES

A complete descriptive matrix of the device characteristics for the Fertility Focus OvuSense as compared to the predicate device, Bioself 2000 (K904211), is shown in Table 7.1. This information demonstrates the **substantial equivalence** between the Fertility Focus OvuSense and the predicate Bioself 2000 (K904211).

4. ARE PERFORMANCE DATA AVAILABLE TO ASSESS EQUIVALENCE?..... YES

5. DOES THE PERFORMANCE DATA DEMONSTRATE EQUIVALENCE?..... YES

The verification testing performed for the Fertility Focus OvuSense demonstrates that the device performs as intended. The Fertility Focus OvuSense complies with the requirements of ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature. Electrical testing all passed as demonstrated in Section 9. Software level of concern is Minor and evidence of software testing is included in Section 5.

The Fertility Focus OvuSense performs (in use) identical to the predicate ovulation monitor with a vaginal probe to collect basal body temperature data. Fertility Focus OvuSense is demonstrated to be **substantially equivalent** to the Bioself 2000 (K904211) predicate device.

Clinical testing was performed as validation that Fertility Focus OvuSense demonstrates that the device performs as the user expects. Comparisons were made to ultrasound detection as the gold standard for predicting the fertility cycle.

Performance testing does not raise any new questions with regards to safety or effectiveness when compared to the predicate device.

See Section 8 Summary of Performance Testing for a summary of the testing performed.

6. REASON FOR PREMARKET NOTIFICATION?

To obtain clearance for the new OvuSense Advanced Fertility Monitoring System, as described in detail in Section 4.

Substantial Equivalence

The Fertility Focus OvuSense is substantially equivalent to the Bioself 2000 (K904211) ovulation monitor. The Fertility Focus OvuSense has similar indications/intended use statements, principles of operation, and technological characteristics as the predicate device.

Bench and clinical testing demonstrates that the Fertility Focus OvuSense is functionally equivalent to the predicate device and does not raise any new questions with regards to safety and effectiveness when compared to the predicate device (see Section 8 for a summary of the testing results). Table 7.1 below presents the similarities and differences.

TABLE 7.1
PREDICATE EQUIVALENCE MATRIX

	Feature	Fertility Focus OvuSense Proposed Device	Bioself 2000 (K904211) Predicate Device	Supporting Documents
General	Equivalent Statement	The Fertility Focus OvuSense is substantially equivalent to the Bioself 2000 (K904211) ovulation monitor. The Fertility Focus OvuSense has similar indications/intended use statements, principles of operation, and technological characteristics as the predicate device.		See Section 4 in this submission for details
	510K Reference	TBD	K904211	Same See **Attachment T** for Predicate Device Information
	Manufacturer	(b)(4) CCI [redacted]	Bioself, Inc.	
	Product Trade Name	OvuSense Advanced Fertility Monitoring System	Bioself 2000 Fertility Indicator	
	Classification #	Unclassified	Unclassified	
	Classification Name	Device, fertility diagnostic, proceptive	Device, fertility diagnostic, proceptive	
	Product Code	LHD	LHD	

	Feature	Fertility Focus OvuSense Proposed Device	Bioself 2000 (K904211) Predicate Device	Supporting Documents
Labeling	Indications for Use Statement	The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).	The Bioself 2000 is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).	Substantially Equivalent See **Attachment T** for Predicate Device Information
	Patient Population/ Environment of Use	Home use by a woman who has menstrual cycles and is interested in her ovulation pattern. OTC device.	Home use by a woman who has menstrual cycles and is interested in her ovulation pattern. OTC device.	
Device Description	Device Description	The OvuSense consists of a Personal Sensor and a Reader (with LCD display). The Personal Sensor records temperature via the vagina continuously throughout the night. The OvuSense Reader has an LCD display that shows level of fertility, and five buttons for the user to interact with the Reader. The LCD display shows user input data and fertility/ovulation information.	Probe allows woman to record daily temperature by mouth, rectum, or vagina upon waking. Bioself is a small portable electronic device, composed of a probe to record temperature, three indicator lights that tell her the daily level of fertility, a red push button to record the beginning of her period, a black push button to access lastly recorded temperatures, and an LCD display to read measured temperature.	Substantially Equivalent See **Attachment T** for Predicate Device Information
	Principles of Operation	Measures basal body temperature via vagina (b)(4) [redacted] overnight, during the non-menstruating period of a woman's cycle. Uses the data and applies a software algorithm to calculate the start and end of the fertile phase.	Measures basal body temperature via vagina, mouth, or rectum via manual measurement upon waking. Uses a software algorithm to calculate the start and end of the fertile phase.	

	Feature	Fertility Focus OvuSense Proposed Device	Bioself 2000 (K904211) Predicate Device	Supporting Documents
	User Interaction	User interacts with menus/prompts displayed on LCD screen via five buttons on Reader device.	User interacts with device via visual light cues and two buttons on device.	
	Result Reading	Fertility prediction is calculated by software algorithm and displayed to user on LCD screen of Reader. Data is displayed as specific range of days for fertility, as well as a graph.	Fertility prediction is calculated by software algorithm and displayed to user via green (infertile), red (fertile), and red flashing (very fertile) indicator lights.	
Device Construction	Materials	Reader: Plastic casing Personal Sensor: Plastic casing	Plastic casing with metal probe	Substantially Equivalent See **Attachment C** for OvuSense Materials Information and **Attachment T** for Predicate Device Information
	Power Supply	120V a/c connector	NA	No new questions of Safety and Effectiveness See Section 8 for Performance Testing
	Battery	Rechargeable internal 9VDC battery	Uses three standard alkaline batteries of 1.5V (AAA/LR03)	
	Data Memory	Displays fertility information for up to past three menstrual cycles	Displays fertility information for up to past 12 menstrual cycles	
	Fertility Display	Fertility displayed as a specific range of days for fertility as well as in graph format on LCD screen.	Fertility displayed via LED lights on device. Can receive printouts in graph format after telephone transmission of data.	

	Feature	Fertility Focus OvuSense Proposed Device	Bioself 2000 (K904211) Predicate Device	Supporting Documents
Sterilization & Other	Packaging	Personal Sensor in Tyvek pouch, shipping carton	Unknown	See Section 8 Performance Testing
	Sterilization	Non-Sterile	Non-Sterile	
	Biocompatibility	Materials have been assessed based on ISO 10993-1:2003	Materials have been assessed based on ISO 10993-1:2003	See **Attachments D, E, F,** and **G** for Fertility Focus Biocompatibility Testing

Other reference devices for OvuSense which are legally marketed with substantially equivalent attributes as OvuSense are:

B-D Digital Basal Thermometer K945427 (ovulation determining device obtained from basal body temperature).
Clearblue – Clearplan Easy Fertility Monitor K981207 and K99022 (ovulation determining device). Current product is known as Clearblue™ Fertility Monitor.
VitalSense. K033534 (for remote data download)
Duofertility K102499 (for continuous temperature monitoring)

8. SUMMARY OF PERFORMANCE TESTING

8.1 SUMMARY OF PERFORMANCE TESTING

A series of tests and evaluations was conducted in support of the design verification of the OvuSense Advanced Fertility Monitoring System.

Electrical Testing is included in Section 9. Electrical testing, EMC, and radio testing studies were conducted to demonstrate OvuSense Advanced Fertility Monitoring System conformance to UL guidelines. See **Attachment O** for OvuSense electrical, EMC, and radio testing reports.

Software level of concern of Minor is documented in Section 5. See software specification requirements, traceability analysis, and verification and validation results.

Clinical validation is presented in Section 10.

Fertility Focus verification functional testing complies with the FDA recognized standard ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature.

The tables that follow provide non-clinical in-vitro bench test results for OvuSense device testing to ASTM E1112:2011 for performance (range, accuracy, precision and repeatability).

Results of all testing provided in this Submission provide demonstration with verification and validation studies that the OvuSense Advanced Fertility Monitoring System is effective for use as it performs as intended and is safe as provided by the electrical testing.

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

9.1 UTILIZATION OF STANDARDS

Electrical testing, EMC, and radio testing studies were conducted by (b)(4) CCI [redacted]) to demonstrate OvuSense Advanced Fertility Monitoring System conformance to UL guidelines. See **Attachment O** for OvuSense electrical, EMC, and radio testing reports.

TABLE 9.1
OVUSENSE ELECTRICAL, EMC AND RADIO TESTING

Testing Standard	Result
Electrical Testing to BS EN60601-1-4:2000 Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.	Compliant
EMC Testing to EN60601-1-2:2007 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests Report No: TES 004397-01	Compliant
EMC Testing to EN301 489-3 v1.4.1 Electromagnetic Compatibility and Radio Spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3: Specific Conditions for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz Report No: TES 004397-01	Compliant
Electrical Safety to IEC60601-1:2006 Medical equipment. Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Report No: TRA-004397-34-02A	Compliant
Radio Testing to EN302 291 v1.1.1 Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Close Range Inductive Data Communication equipment operating at 13,56 MHz; Part 2: Harmonized EN under article 3.2 of the R&TTE Directive. Report No: TES-004397WEU1	Compliant

9.2 SUMMARY OF ELECTRICAL TESTING

EMC Testing
EMC testing of OvuSense Reader and Personal Sensor according to the specifications EN60601-1-2:2007 and ETSI EN201-489-3 V1.4.1 (2002-08) is documented in Report TES 004397-01.

EMC testing was conducted by (b)(4) CCI [redacted]

The purpose of the test - electrocompatibility – Emissions and Immunity.

Equipment under test (EUT) - OvuSense Reader and OvuSense Sensor.

Test Results - measured as compliant.

Test date – (b)(4) CCI [redacted]

Radio Test Report: ETSI EN302 291-2 V1.1.1
Radio test report is documented in Document No. TES-004397WEU1 according to the specification ETSI EN302 291-2 V1.1.1; conducted by (b)(4) CCI [redacted]

Equipment under test – OvuSense.
Test date - (b)(4) CCI [redacted]

Essential Radio Test suite and test result summary is provided in Appendix A of the report TES-004397WEU1.

Summary of compliance – The samples as assessed satisfied the relevant requirements of ETS1 EN 302 291-2 V1.1.1 as detailed in section 2.1 of the above report.

Radio Test Report: CFR47 Part 15C 15.225: July 2008
Radio test report is documented in Document No. TES-00397WUS1 according to the specification CFR47 Part 15C 15.225: July 2008; conducted by (b)(4) CCI [redacted]

Equipment under test – OvuSense.

FCCID – Z8YM009-V1

Purpose of test - Certification

Test date - (b)(4) CCI [redacted].

Full details of test results are contained within Appendix A of the report TES-00397WUS1.

(b)(4) CCI

Safety of Electrical Equipment

Safety of electrical equipment according to the IEC 60601-1 (Medical electrical equipment) is documented in report no. (b)(4) 004397-34-02A; conducted by testing laboratory, (b)(4) CCI

Test item – OvuSense (Fertility Monitor) with ratings IN:100-240Vac, 0.4A, 50/60Hz. OUT: 9Vdc, 0.88A.

The following tests were performed:

- Clause 4.11 Power Input
- Clause 7 Marking, documentation and marking durability
- Clause 8 Protection against electrical hazards (including discharge; grounding impedance; Leakage current; humidity treatment; electrical strength and components)
- Clause 9 Protection against mechanical hazard
- Clause 11 Protection against excessive temperature
- Clause 13 Hazardous situations and fault conditions
- Clause 15 Construction of equipment (mechanical strength).

The product tested was considered to have satisfied the requirements of standard EN60601-1:2006.

10. SUMMARY OF CLINICAL TESTING

10.1 UTILIZATION OF STANDARDS

Fertility Focus clinical testing complies with the following FDA-recognized standards and Guidance documents:

- ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice.
- ISO 14971: 2007 Application of Risk Management to Medical Devices.
- FDA Guidance on Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management, July 2000.

10.2 DESIGN VALIDATION TESTING—CLINICAL INVESTIGATION

A design validation study in the form of a clinical trial of the OvuSense Advanced Fertility Monitoring System was conducted on behalf of Fertility Focus to investigate the efficacy of an indwelling temperature monitor to identify and to predict ovulation. The Clinical Investigation Plan, including details on primary and secondary endpoints, chief investigator and investigation center information, study design and plan description, informed consent form, patient instructions, MHRA no objection and REC trial approval is provided with this Submission in **Attachment M**.

For a rationale for the use of comparative reference and predicate devices, see **Attachment Q**.

Introduction

(b)(4) CCI

[redacted]

Design Validation Summary

(b)(4) CCI

[redacted]

Primary Clinical Controls:

1. B-D Digital Basal Thermometer K945427
2. Clearblue™ - Clear Plan Easy Fertility Monitor K981207 and K990223
3. Ultrasound

Use of Proxy Markers and Predicates in OvuSense Design Validation

It is known that the LH peak which occurs just before ovulation is associated with a rise in BBT.

Taking this into account and in order to effectively validate the design of OvuSense, as well as provide accurate comparison with predicate devices or surrogates for those predicate devices it was therefore decided to run a longitudinal, observational comparative study.

The study consisted of comparative measurements of BBT established with single point, oral temperature using a digital thermometer (surrogate for predicate 1 and 2), positive luteinising hormone results obtained using Clearblue urine testing strips (predicate 3), and results from the OvuSense system in conjunction with a "gold standard" measurement of ovulation established using ultrasound foliculometry.

(b)(4) CCI [redacted]

In the design validation the OvuSense (b)(4) CCI who met the study criteria contributed a

(b)(4) CCI [redacted]

Materials and Methods

(b)(4) CCI [redacted]

The OvuSense was tested against the current method of recording BBT using a single oral, waking temperature measurement and identifying ovulation by the 'three over six' rule.[12] [13] The actual day of ovulation will be identified using daily, urinary LH measurements and daily

(b)(4) CCI

[redacted]

(b)(4) CCI

[redacted]

Conclusion

The data demonstrated that the OvuSense system of ovulation detection provided a biologically and statistically significant improvement in ovulation detection compared with the traditional method of oral temperature measurement. (b)(4) CCI [redacted]

See **Attachment R** for OvuSense Clinical Investigation Study Report. See **Attachment S** for an analysis of the ability of OvuSense to detect the fertile period within a current menstrual cycle.

10.3 DISCUSSION AND CONCLUSIONS

In the design validation the OvuSense (b)(4) CCI who met the study criteria contributed ([redacted] During each cycle, they used the OvuSense kept a diary of daily early b morning temperatures and also attended for ultrasound when urinary LH tests became) positive. Statistical analysis was performed by paired t-test and multilevel model approach.

(b)(4) CCI [redacted]

[14] Bland, J.M., Altman, D.G., Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1986. i:307-10.

11. PREDICATE DEVICE INFORMATION

11.1 PREDICATE DEVICE INFORMATION

A copy of the following predicate information is provided in **Attachment T**:

- Bioself 2000 K904211 FDA listing
- Bioself 2000 Product Information
- Bioself 2000 Flyer

12.1 PROPOSED LABELING

OvuSense devices are packaged in three configurations:

- Personal Sensor only (in Tyvek pouch)
- Reader only
- Personal Sensor and Reader-Advanced Fertility Monitoring System

A User Manual is included in each package. See **Attachment L**.

Symbols Used in Fertility Focus Labeling
Symbols used in Fertility Focus labeling conform to standard ISO 15223:2007, Medical Device, Symbols to be used with Medical Device labels, labeling, and information to be supplied Part 1 – General Requirements. This is an FDA recognized standard (FDA Recognition Number: 5-31).

OvuSense Reader
English M010-EN

The OvuSense advanced fertility monitor is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating. OvuSense detects the presence and absence of ovulation, as well as predicting the fertile period for the next monthly cycle.

Quantity	OvuSense Reader	1

Unit 19D
University of Warwick Science Park
Warwick Innovation Centre
Warwick Technology Park
Gallows Hill
Warwick
CV34 6UW
United Kingdom

t: +44(0)1793 848088
f: +44(0)1793 855440
e: service@fertility-focus.com
w: www.ovusense.com
w: www.fertility-focus.com

CE 0123

FIGURE 12.1-1: OvuSense Reader Primary Label

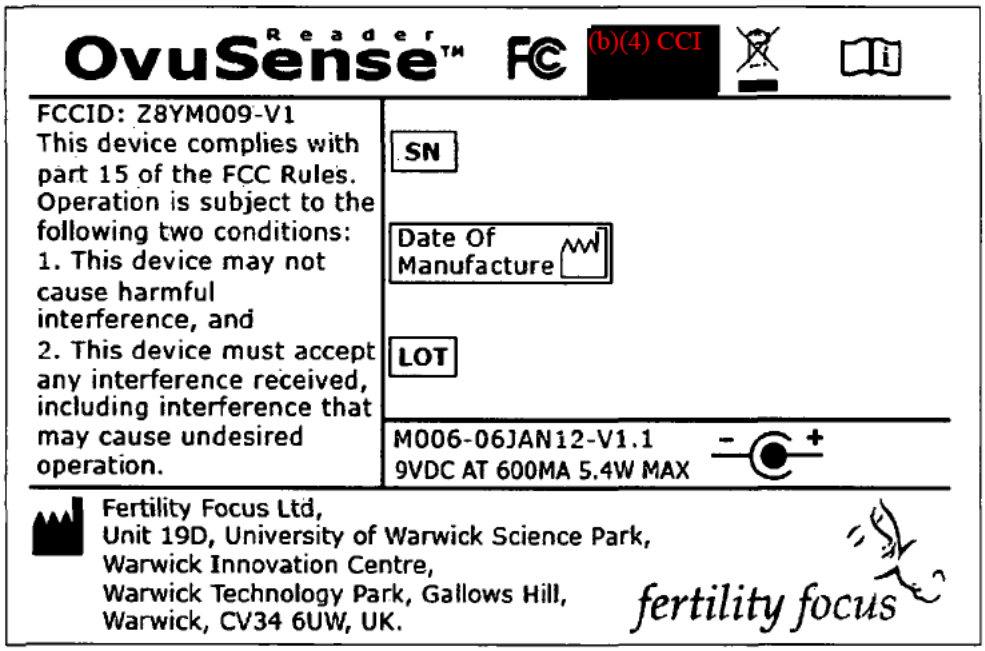


FIGURE 12.1-2: OvuSense Reader Underside of Device Label

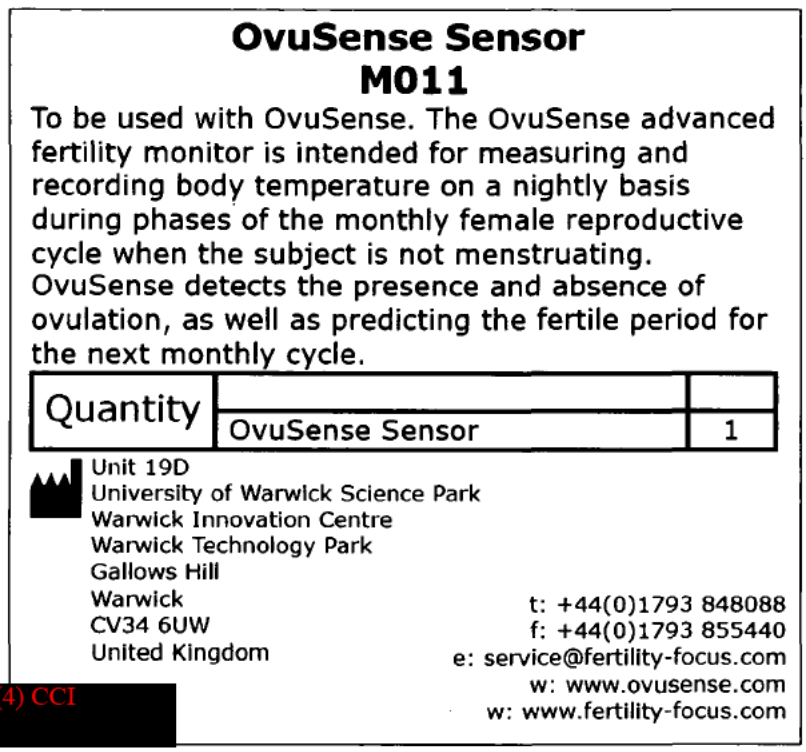


FIGURE 12.1-3: OvuSense Personal Sensor Primary Label

OvuSense Starter Pack-
English M009-EN

The OvuSense advanced fertility monitor is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating. OvuSense detects the presence and absence of ovulation, as well as predicting the fertile period for the next monthly cycle.

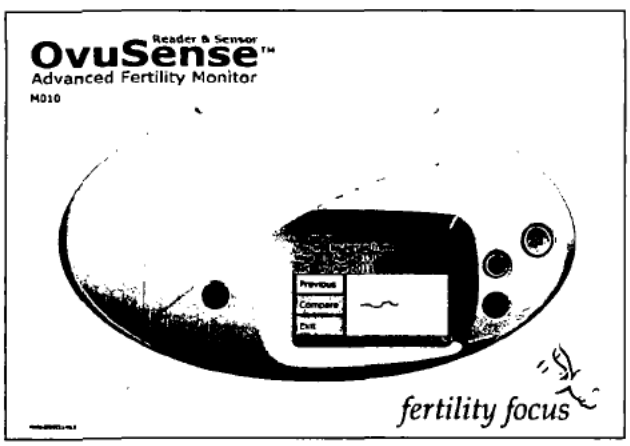
Quantity		
	OvuSense Reader	1
	OvuSense Sensor	1

Unit 19D
University of Warwick Science Park
Warwick Innovation Centre
Warwick Technology Park
Gallows Hill
Warwick
CV34 6UW
United Kingdom

t: +44(0)1793 848088
f: +44(0)1793 855440
e: service@fertility-focus.com
w: www.ovusense.com
w: www.fertility-focus.com

(b)(4) CCI

FIGURE 12.1-4: OvuSense Reader & Personal Sensor Primary Label



OvuSense Reader English
M010-EN

Unit 19D
University of Warwick Science Park
Warwick Innovation Centre
Warwick Technology Park
Gallows Hill
Warwick
CV34 6UW
United Kingdom

t: +44(0)1793 848088
f: +44(0)1793 855440
w: www.ovusense.com
w: www.fertility-focus.com
e: service@fertility-focus.com

(b)(4) CCI

FIGURE 12.1-5: Reader Carton Label

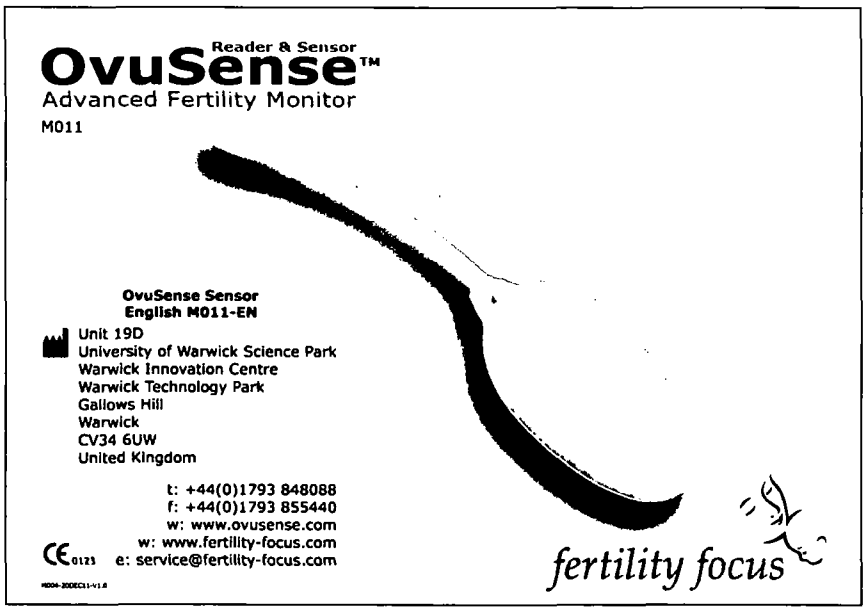


FIGURE 12.1-6: Personal Sensor Carton Label

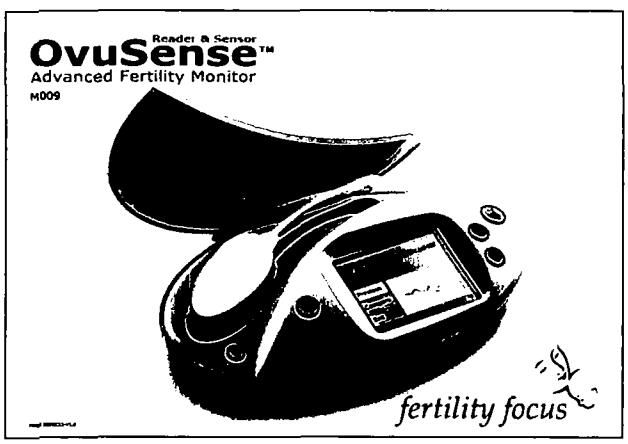


FIGURE 12.1-7: Starter Pack (Reader and Personal Sensor) Carton Label

fertility focus

This 510(k) summary of safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

DATE:	July 31, 2012
APPLICANT:	Fertility Focus Ltd. Mo Aslam, PhD Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW Tel: 044-1494-510272 Email: mo.aslam@fertility-focus.com
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION:	Penny Northcutt, RAC, FRAPS, CQA Regulatory Consultant for Fertility Focus REGSolutions, LLC Tel: 678-428-6978 Fax: 678-513-0937 Email: pennynorthcutt@theregsolutions.com
TRADE NAME:	OvuSense Advanced Fertility Monitoring System
CLASSIFICATION NAME:	Device, fertility diagnostic, proceptive
DEVICE CLASSIFICATION AND PRODUCT CODE:	Pre-amendment, Unclassified Product Code: LHD
PREDICATE DEVICE NAME:	Bioself 2000 Fertility Indicator, K904211

SUBSTANTIAL EQUIVALENCE:
The OvuSense Advanced Fertility Monitoring System is substantially equivalent to the legally marketed Bioself 2000 (K904211) ovulation monitor.

TECNOLOGICAL CHARACTERISTICS:
The OvuSense Advanced Fertility Monitoring System has substantially equivalent technological characteristics when compared to the predicate device. It has substantially equivalent indications for use, software algorithm to calculate ovulation, and principles of

operation. Bench testing, electrical testing, and clinical testing have demonstrated that the OvuSense Advanced Fertility Monitoring System performs effectively as intended and is safe as provided by the electrical testing. The descriptive and technological characteristics are functionally equivalent to the proposed predicate ovulation monitor. Any minor differences do not affect safety or effectiveness of the OvuSense Advanced Fertility Monitoring System.

DESCRIPTION OF THE DEVICE:
The OvuSense Advanced Fertility Monitoring System is intended for measuring and recording core body temperature on a nightly basis during the non-menstruating phases of the monthly female reproductive cycle. The OvuSense Advanced Fertility Monitoring System records basal body temperature over a number of menstrual cycles, then uses this data and applies an algorithm to accurately predict time of ovulation. The OvuSense consists of a Personal Sensor probe, which collects the data, and a Reader (with LCD display), which establish a communication link to the Personal Sensor whereupon the data is transferred to the Reader.

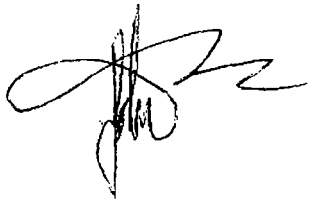
INTENDED USE/INDICATIONS FOR USE:
The OvuSense is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

PERFORMANCE DATA:
A series of performance tests was conducted in support of the design verification of the OvuSense Advanced Fertility Monitoring System in accordance with ASTM E1112:2011 for performance (range, accuracy, precision and repeatability). In addition, electrical testing in accordance with EN60601-1-4:2000, EN60601-1-2:2007, EN301 489-3 v1.4.1, IEC60601-1:2006, and EN302 291 v1.1.1 was conducted to demonstrate electrical safety. Clinical studies were conducted to confirm design validation.

CONCLUSION:
Based on the verification performance and clinical validation, it can be concluded that the OvuSense Advanced Fertility Monitoring System is equivalent to the Bioself 2000 (K904211) with respect to intended use, principles of operation, and technological characteristics.

TRUTHFUL AND ACCURATE STATEMENT

Pursuant to 21 CFR 807.87(j) I certify that in my capacity as the Technical Director for Fertility Focus Limited, I believe to the best of my knowledge, that all data and information submitted in this premarket notification are truthful and accurate and that no material fact has been omitted.



Dr Mo Aslam

Technical Director

Fertility Focus Limited

Warwick, United Kingdom

LITERATURE REFERENCES

STATISTICAL METHODS FOR ASSESSING AGREEMENT BETWEEN TWO METHODS OF CLINICAL MEASUREMENT

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SUMMARY

In clinical measurement comparison of a new measurement technique with an established one is often needed to see whether they agree sufficiently for the new to replace the old. Such investigations are often analysed inappropriately, notably by using correlation coefficients. The use of correlation is misleading. An alternative approach, based on graphical techniques and simple calculations, is described, together with the relation between this analysis and the assessment of repeatability.

(*Lancet*, 1986; **i:** 307-310)

INTRODUCTION

Clinicians often wish to have data on, for example, cardiac stroke volume or blood pressure where direct measurement without adverse effects is difficult or impossible. The true values remain unknown. Instead indirect methods are used, and a new method has to be evaluated by comparison with an established technique rather than with the true quantity. If the new method agrees sufficiently well with the old, the old may be replaced. This is very different from calibration, where known quantities are measured by a new method and the result compared with the true value or with measurements made by a highly accurate method. When two methods are compared neither provides an unequivocally correct measurement, so we try to assess the degree of agreement. But how?

The correct statistical approach is not obvious. Many studies give the product-moment correlation coefficient (r) between the results of the two measurement methods as an indicator of agreement. It is no such thing. In a statistical journal we have proposed an alternative analysis, [1] and clinical colleagues have suggested that we describe it for a medical readership.

Most of the analysis will be illustrated by a set of data (Table 1) collected to compare two methods of measuring peak expiratory flow rate (PEFR).

SAMPLE DATA

The sample comprised colleagues and family of J.M.B. chosen to give a wide range of PEFR but in no way representative of any defined population. Two measurements were made with a Wright peak flow meter and two with a mini Wright meter, in random order. All measurements were taken by J.M.B., using the same two instruments. (These data were collected to demonstrate the statistical method and provide no evidence on the comparability of these two instruments.) We did not repeat suspect readings and took a single reading as our measurement of PEFR. Only the first measurement by each method is used to illustrate the comparison of methods, the second measurement being used in the study of repeatability.

PLOTTING DATA

The first step is to plot the data and draw the line of equality on which all points would lie if the two meters gave exactly the same reading every time (fig 1). This helps the eye in gauging the degree of agreement between measurements, though, as we shall show, another type of plot is more informative.

PEFR MEASURED WITH WRIGHT PEAK FLOW AND MINI WRIGHT PEAK FLOW METER

	Wright peak flow meter		Mini Wright peak flow meter	
	First PEFR	Second PEFR	First PEFR	Second PEFR
Subject	(l/min)	(l/mi)	(l/min)	(l/min)
1	494	490	512	525
2	395	397	430	415
3	516	512	520	508
4	434	401	428	444
5	476	470	500	500
6	557	611	600	625
7	413	415	364	460
8	442	431	380	390
9	650	638	658	642
10	433	429	445	432
11	417	420	432	420
12	656	633	626	605
13	267	275	260	227
14	478	492	477	467
15	178	165	259	268
16	423	372	350	370
17	427	421	451	443

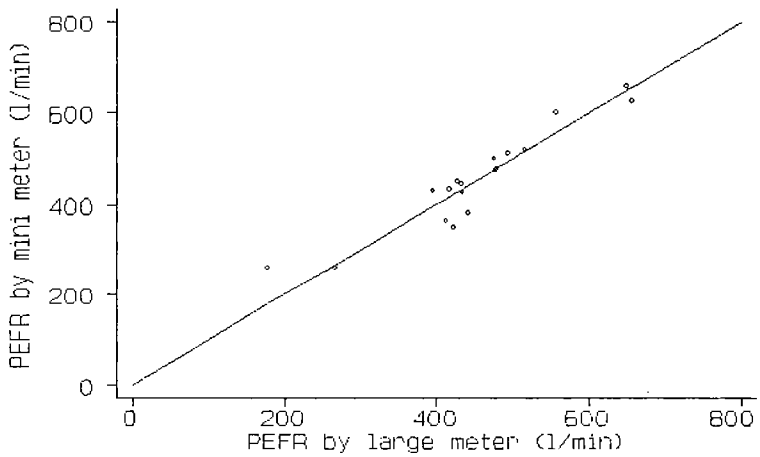

Fig 1. PEFR measured with large Wright peak flow meter and mini Wright peak flow meter, with line of equality.

INAPPROPRIATE USE OF CORRELATION COEFFICIENT

The second step is usually to calculate the correlation coefficient (r) between the two methods. For the data in fig 1, $r = 0.94$ ($p < 0.001$). The null hypothesis here is that the measurements by the two methods are not linearly related. The probability is very small and we can safely conclude that PEFR measurements by the mini and large meters are related. However, this high correlation does not mean that the two methods agree:

(1) r measures the strength of a relation between two variables, not the agreement between them. We have perfect agreement only if the points in fig 1 lie along the line of equality, but we will have perfect correlation if the points lie along any straight line.

(2) A change in scale of measurement does not affect the correlation, but it certainly affects the agreement. For example, we can measure subcutaneous fat by skinfold calipers. The calipers will measure two thicknesses of fat. If we were to plot calipers measurement against half-calipers measurement, in the style of fig 1, we should get a perfect straight line with slope 2.0. The correlation would be 1.0, but the two measurements would not agree — we could not mix fat thicknesses obtained by the two methods, since one is twice the other.

(3) Correlation depends on the range of the true quantity in the sample. If this is wide, the correlation will be greater than if it is narrow. For those subjects whose PEFR (by peak flow meter) is less than 500 l/min, r is 0.88 while for those with greater PEFRs r is 0.90. Both are less than the overall correlation of 0.94, but it would be absurd to argue that agreement is worse below 500 l/min and worse above 500 l/min than it is for everybody. Since investigators usually try to compare two methods over the whole range of values typically encountered, a high correlation is almost guaranteed.

(4) The test of significance may show that the two methods are related, but it would be amazing if two methods designed to measure the same quantity were not related. The test of significance is irrelevant to the question of agreement.

(5) Data which seem to be in poor agreement can produce quite high correlations. For example, Serfontein and Jaroszewicz [2] compared two methods of measuring gestational age. Babies with a gestational age of 35 weeks by one method had gestations between 34 and 39.5 weeks by the other, but r was high (0.85). On the other hand, Oldham et al. [3] compared the mini and large Wright peak flow meters and found a correlation of 0.992. They then connected the meters in series, so that both measured the same flow, and obtained a "material improvement" (0.996). If a correlation coefficient of 0.99 can be materially improved upon, we need to rethink our ideas of what a high correlation is in this context. As we show below, the high correlation of 0.94 for our own data conceals considerable lack of agreement between the two instruments.

MEASURING AGREEMENT

It is most unlikely that different methods will agree exactly, by giving the identical result for all individuals. We want to know by how much the new method is likely to differ from the old: if this is not enough to cause problems in clinical interpretation we can replace the old method by the new or use the two interchangeably. If the two PEFR meters were unlikely to give readings which differed by more than, say, 10 l/min, we could replace the large meter by the mini meter because so small a difference would not affect decisions on patient management. On the other hand, if the meters could differ by 100 l/min, the mini meter would be unlikely to be satisfactory. How far apart measurements can be without causing difficulties will be a question of judgment. Ideally, it should be defined in advance to help in the interpretation of the method comparison and to choose the sample size.

The first step is to examine the data. A simple plot of the results of one method against those of the other (fig 1) though without a regression line is a useful start but usually the data points will be clustered near the line and it will be difficult to assess between-method differences. A plot of the difference between the methods against their mean may be more informative. Fig 2 displays considerable lack of agreement between the large and mini meters, with discrepancies of up to 80 l/min, these differences are not obvious from fig 1. The plot of difference against mean also allows us to investigate any possible relationship between the measurement error and the true value. We do not know the true value, and the mean of the two measurements is the best estimate we have. It would be a mistake to plot the difference against either value separately because the difference will be related to each, a well-known statistical artefact. [4]

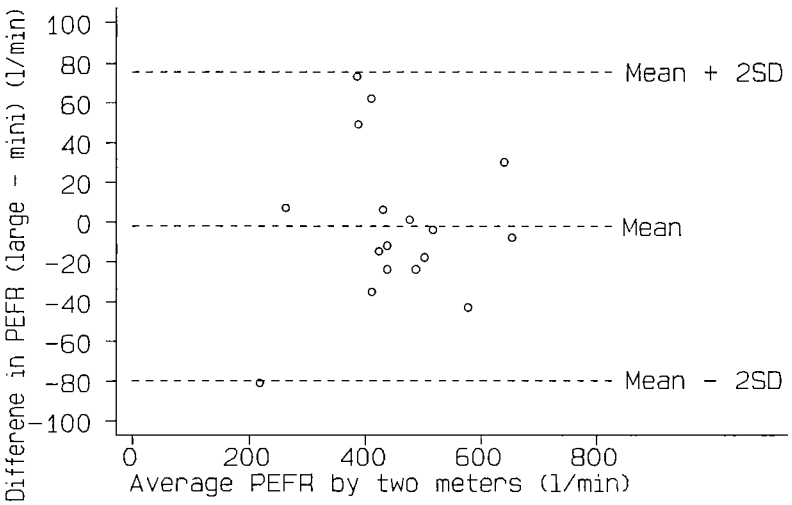

Fig 2. Difference against mean for PEFR data.

For the PEFR data, there is no obvious relation between the difference and the mean. Under these circumstances we can summarise the lack of agreement by calculating the bias, estimated by the mean difference $\bar{d}$ and the standard deviation of the differences (s). If there is a consistent bias we can adjust for it by subtracting $\bar{d}$ from the new method. For the PEFR data the mean difference (large meter minus small meter) is -2.1 l/min and s is 38.8 l/min. We would expect most of the differences to lie between $\bar{d}-2s$ and $\bar{d}+2s$ (fig 2). If the differences are Normally distributed (Gaussian), 95% of differences will lie between these limits (or, more precisely, between $\bar{d}-1.96s$ and $\bar{d}+1.96s$). Such differences are likely to follow a Normal distribution because we have removed a lot of the variation between subjects and are left with the measurement error. The measurements themselves do not have to follow a Normal distribution, and often they will not. We can check the distribution of the differences by drawing a histogram. If this is skewed or has very long tails the assumption of Normality may not be valid (see below).

Provided differences within $\bar{d} \pm 2s$ would not be clinically important, we could use the two measurement methods interchangeably. We shall refer to these as the "limits of agreement". For the PEFR data we get:

$$\bar{d}-2s = -2.1-(2\times 38.8) = -79.7 \text{ l/min}$$

$$\bar{d}+2s = -2.1+(2\times 38.8) = -75.5 \text{ l/min}$$

Thus, the mini meter may be 80 l/min below or 76 l/min above the large meter, which would be unacceptable for clinical purposes. This lack of agreement is by no means obvious in fig 1.

PRECISION OF ESTIMATED LIMITS OF AGREEMENT

The limits of agreement are only estimates of the values which apply to the whole population. A second sample would give different limits. We might sometimes wish to use standard errors and confidence intervals to see how precise our estimates are, provided the differences follow a distribution which is approximately Normal. The standard error of $\bar{d}$ is $\sqrt{s^2/n}$, where n is the sample size, and the standard error of $\bar{d}-2s$ and $\bar{d}+2s$ is about $\sqrt{3s^2/n}$. 95% confidence intervals can be calculated by finding the appropriate point of the t distribution with $n-1$ degrees of freedom, on most tables the columns marked 5% or 0.05,

and then the confidence interval will be from the observed value minus t standard errors to the observed value plus t standard errors.

For the PEFR data $s = 38.8$. The standard error of $\bar{d}$ is thus 9.4, For the 95% confidence interval we have 16 degrees of freedom and $t = 2.12$. Hence the 95% confidence interval for the bias is $-2.1-(2.12\times 9.4)$ to $-2.1+(2.12\times 9.4)$, giving -22.0 to 17.8 l/min. The standard error of the limit $\bar{d}-2s$ is 16.3 l/min. The 95% confidence interval for the lower limit of agreement is $-79.7-(2.12\times 16.3)$ to $-79.7+(2.12\times 16.3)$, giving -114.3 to -45.1 l/min. For the upper limit of agreement the 95% confidence interval is 40.9 to 110.1 l/min. These intervals are wide, reflecting the small sample size and the great variation of the differences. They show, however, that even on the most optimistic interpretation there can be considerable discrepancies between the two meters and that the degree of agreement is not acceptable.

EXAMPLE SHOWING GOOD AGREEMENT

Fig 3 shows a comparison of oxygen saturation measured by an oxygen saturation monitor and pulsed oximeter saturation, a new non-invasive technique. [5] Here the mean difference is 0.42 percentage points with 95% confidence interval 0.13 to 0.70. Thus pulsed oximeter saturation tends to give a lower reading, by between 0.13 and 0.70. Despite this, the limits of agreement (-2.0 and 2.8) are small enough for us to be confident that the new method can be used in place of the old for clinical purposes.

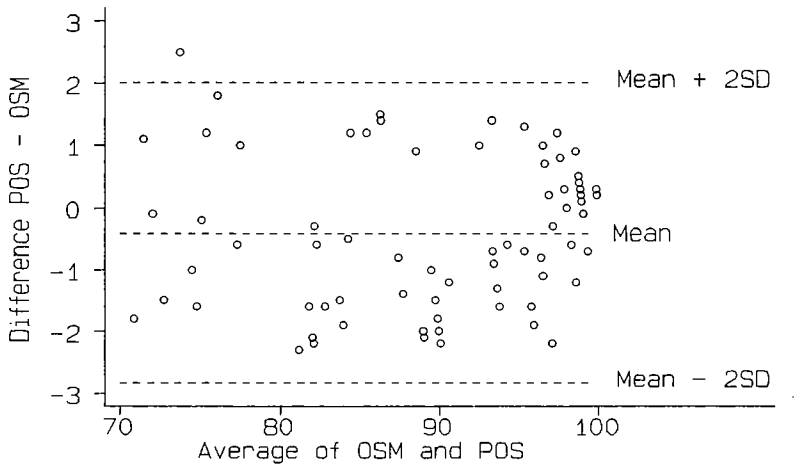

Fig 3. Oxygen saturation monitor and pulsed saturation oximeter

RELATION BETWEEN DIFFERENCE AND MEAN

In the preceding analysis it was assumed that the differences did not vary in any systematic way over the range of measurement. This may not be so. Fig 4 compares the measurement of mean velocity of circumferential fibre shortening (VCF) by the long axis and short axis in M-mode echocardiography. [6] The scatter of the differences increases as the VCF increases. We could ignore this, but the limits of agreement would be wider apart than necessary for small VCF and narrower than they should be for large VCF. If the differences are proportional to the mean, a logarithmic transformation should yield a picture more like that of figs 2 and 4, and we can then apply the analysis described above to the transformed data.

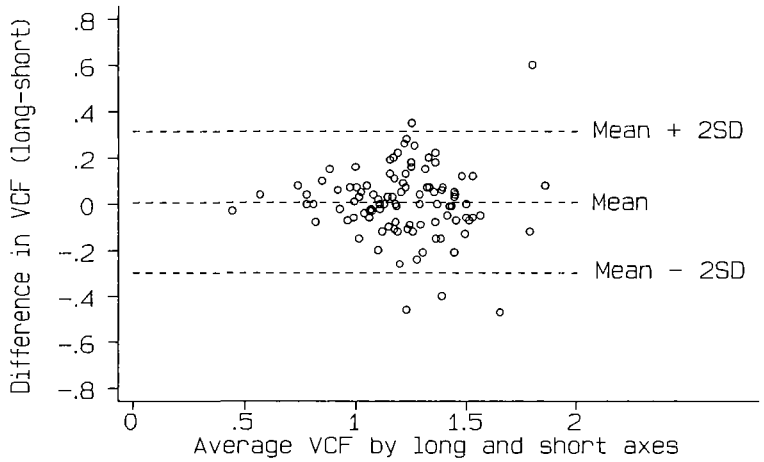

Fig 4. Mean VCF by long and short axis measurements.

Fig 5 shows the log-transformed data of fig 4. This still shows a relation between the difference and the mean VCF, but there is some improvement. The mean difference is 0.003 † on the log scale and the limits of agreement are -0.098 † and 0.106.† However, although there is only negligible bias, the limits of agreement have somehow to be related to the original scale of measurement. If we take the antilogs of these limits, we get 0.80 and 1.27. However, the antilog of the difference between two values on a log scale is a dimensionless ratio. The limits tell us that for about 95% of cases the short axis measurement of VCF will be between 0.80 and 1.27 times the long axis VCF. Thus the short axis measurement may differ from the long axis measurement by 20% below to 27% above. (The log transformation is the only transformation giving back-transformed differences which are easy to interpret, and we do not recommend the use of any other in this context.)

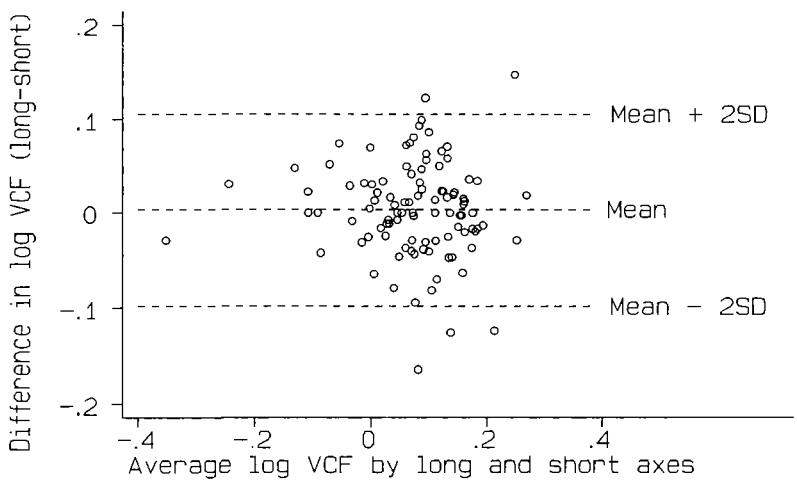

Fig 5. Data of fig 4 after logarithmic transformation.

† These numbers were incorrectly printed as 0.008, -0.226, and 0.243 in the *Lancet*. This mistake arose because when revising the paper we dithered over whether to use natural logs or logs to base 10 and got hopelessly confused.

Sometimes the relation between difference and mean is more complex than that shown in fig 4 and log transformation does not work. Here a plot in the style of fig 2 is very helpful in comparing the methods. Formal analysis, as described above, will tend to give limits of agreement which are too far apart rather than too close, and so should not lead to the acceptance of poor methods of measurement.

REPEATABILITY

Repeatability is relevant to the study of method comparison because the repeatabilities of the two methods of measurement limit the amount of agreement which is possible. If one method has poor repeatability — i.e. there is considerable variation in repeated measurements on the same subject — the agreement between the two methods is bound to be poor too. When the old method is the more variable one, even a new method which is perfect will not agree with it. If both methods have poor repeatability, the problem is even worse.

The best way to examine repeatability is to take repeated measurements on a series of subjects. The table shows paired data for PEFR. We can then plot a figure similar to fig 2, showing differences against mean for each subject. If the differences are related to the mean, we can apply a log transformation. We then calculate the mean and standard deviation of the differences as before. The mean difference should here be zero since the same method was used. (If the mean difference is significantly different from zero, we will not be able to use the data to assess repeatability because either knowledge of the first measurement is affecting the second or the process of measurement is altering the quantity.) We expect 95% of differences to be less than two standard deviations. This is the definition of a repeatability coefficient adopted by the British Standards Institution. [7] If we can assume the main difference to be zero this coefficient is very simple to estimate: we square all the differences, add them up, divide by n, and take the square root, to get the standard deviation of the differences.

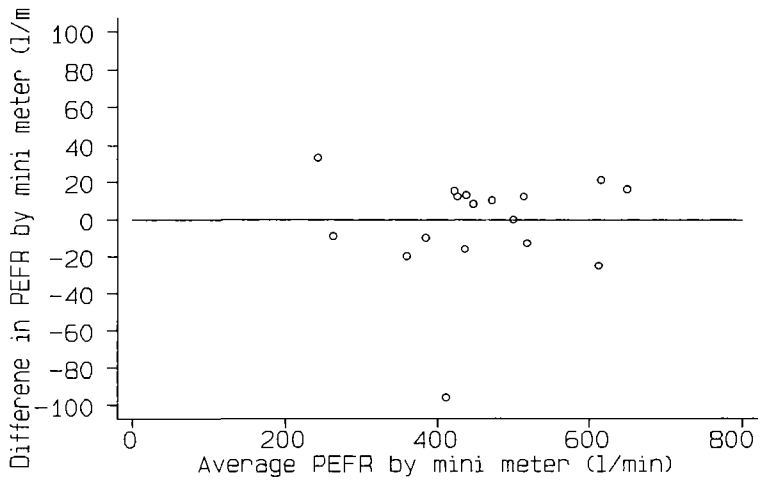

Fig 6. Repeated measures of PEFR using mini Wright peak flow meter.

Fig 6 shows the plot for pairs of measurements made with the mini Wright peak flow meter. There does not appear to be any relation between the difference and the size of the PEFR. There is, however, a clear outlier. We have retained this measurement for the analysis, although we suspect that it was technically unsatisfactory. (In practice, one could omit this subject.) The sum of the differences squared is 13479 so the standard deviation of differences between the 17 pairs of repeated measurements is 28.2 l/min. The coefficient of repeatability

is twice this, or 56.4 l/min for the mini meter. For the large meter the coefficient is 43.2 l/min.

If we have more than two repeated measurements the calculations are more complex. We plot the standard deviation of the several measurements for that subject against their mean and then use one-way analysis of variance, [8] which is beyond the scope of this article.

MEASURING AGREEMENT USING REPEATED MEASUREMENTS

If we have repeated measurements by each of the two methods on the same subjects we can calculate the mean for each method on each subject and use these pairs of means to compare the two methods using the analysis for assessing agreement described above. The estimate of bias will be unaffected, but the estimate of the standard deviation of the differences will be too small, because some of the effect of repeated measurement error has been removed. We can correct for this. Suppose we have two measurements obtained by each method, as in the table. We find the standard deviation of differences between repeated measurements for each method separately, s_1 and s_2, and the standard deviation of the differences between the means for each method, s_D. The corrected standard deviation of differences, s_c, is $\sqrt{s_D^2 + \frac{1}{4}s_1^2 + \frac{1}{4}s_2^2}$. This is approximately $\sqrt{2s_D^2}$, but if there are differences between the two methods not explicable by repeatability errors alone (i.e. interaction between subject and measurement method) this approximation may produce an overestimate. For the PEFR, we have $s_D = 33.2$, $s_1 = 21.6$, $s_2 = 28.2$ ‡ l/min. s_c is thus $\sqrt{33.2^2 + \frac{1}{4} \times 21.6^2 + \frac{1}{4} \times 28.2^2}$ or 37.7 l/min. Compare this with the estimate 38.8 l/min which was obtained using a single measurement. On the other hand, the approximation $\sqrt{2s_D^2}$ gives an overestimate (47.0 l/min).

DISCUSSION

In the analysis of measurement method comparison data, neither the correlation coefficient (as we show here) nor techniques such as regression analysis [1] are appropriate. We suggest replacing these misleading analyses by a method that is simple both to do and to interpret. Further, the same method may be use to analyse the repeatability of a single measurement method or to compare measurements by two observers.

Why has a totally inappropriate method, the correlation coefficient, become almost universally used for this purpose?. Two processes may be at work here --- namely, pattern recognition and imitation. A likely first step in the analysis of such data is to plot a scatter diagram (fig 1). A glance through almost any statistical textbook for a similar picture will lead to the correlation coefficient as a method of analysis of such a plot, together with a test of the null hypothesis of no relationship. Some texts even use pairs of measurements by two different methods to illustrate the calculation of r. Once the correlation approach has been published, others will read of a statistical problem similar to their own being solved in this way and will use the same technique with their own data. Medical statisticians who ask "why did you use this statistical method?" will often be told "because this published paper used it". Journals could help to rectify this error by returning for reanalysis papers which use incorrect statistical techniques. This may be a slow process. Referees, inspecting papers in which two methods of measurement have been compared, sometimes complain if no correlation coefficients are provided, even when the reasons for not doing so are given.

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‡ This was incorrectly printed as s_c in the *Lancet* and in *Biochimica Clinica*.

We thank of our colleagues for their interest and assistance, including Dr David Robson who first brought the problem to us, Dr P. D'Arbela and Dr H. Seeley for the use of their data; and Mrs S Stevens for typing the manuscript.

REFERENCES

1. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *The Statistician* 1983; **32**, 307-317.

2. Serfontein GL, Jaroszewicz AM. Estimation of gestational age at birth: comparison of two methods. *Arch Dis Child* 1978; **53**: 509-11.

3. Oldham HG, Bevan MM, McDermott M. Comparison of the new miniature Wright peak flow meter with the standard Wright peak flow meter. *Thorax* 1979; **34**: 807-08.

4. Gill JS, Zezulka AV, Beevers DG, Davies P. Relationship between initial blood pressure and its fall with treatment. *Lancet* 1985; **i**: 567-69.

5. Tytler JA, Seeley HF. The Nellcor N-101 pulse oximeter - a clinical-evaluation in anesthesia and intensive-care. *Anaesthesia* 1986; **41**: 302-305.

6. D'Arbela PG, Silayan ZM, Bland JM. Comparability of M-mode echocardiographic long axis and short axis left ventricular function derivatives. *British Heart Journal* 1986; **56**: 445-9.

7. British Standards Institution. *Precision of test methods 1: Guide for the determination and reproducibility for a standard test method (BS 597, Part 1).* London: BSI (1975).

8. Armitage P. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1971: chap 7.

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Daily Fecundability: First Results from a New Data Base

Bernardo Colombo

Guido Masarotto

Daily Fecundability: First Results from a New Data Base

Bernardo Colombo[1]

Guido Masarotto[2]

on Behalf of the Menstrual Cycle Fecundability Study Group [Note 1]

Abstract

This multicentre study has produced a database of 7017 menstrual cycles contributed by 881 women. It provides improved knowledge on length and location of the "fertile window" (identified as of up to 12 days duration) and the pattern and level of daily conception probability. The day of ovulation was identified in each cycle from records of basal body temperature and mucus symptoms. By referencing days of intercourse to the surrogate ovulation markers, estimates of daily fecundability were computed either directly or by the Schwartz model, both for single and multiple acts of intercourse in the fertile window. The relationship between coital pattern and fecundability has been explored. Univariate analysis underlines the significant link with fecundability only of the woman's reproductive history.

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1. Introduction

In healthy non-contracepting sexually active couples fecundability, probability of conceiving a pregnancy during a menstrual cycle [Gini 1924, Gini 1928], depends on behaviour as well as physiology. Spermatozoa with the capability of fertilising the egg must already be present in the woman's reproductive tract at the time the egg is released at ovulation or must arrive there soon after. Number and timing of acts of intercourse in the cycle are an important factor. The width of the "fertile" window around ovulation, that is the number of days during which intercourse has a non-zero probability of resulting in conception, is uncertain. Widely diverging figures have been proposed in the literature, ranging from less than two to more than ten days [Glass and Grebenik 1954, Potter 1961, James 1963, Marshall 1967, Lachenbruch 1967, Glasser and Lachenbruch 1968, Barrett and Marshall 1969, Barrett 1971, Loevner 1976, Vollman 1977, Schwartz et al 1979, Trussell 1979, Schwartz, MacDonald, and Heuchel 1980, Royston 1982, Bongaarts and Potter 1983, World Health Organization 1983, World Health Organization 1985, Potter and Millman 1985, Bremme 1991, Weinberg, Gladen, and Wilcox 1994, Trussell 1996, Masarotto and Romualdi 1997, Weinberg et al 1998, Wilcox, Weinberg, and Baird 1998, Sinai, Jennings, and Arévalo 1999, Dunson et al 1999]. These estimates depend on data analysed, on conjectures accepted, on evaluations made with different approaches. Precise information on the pattern of daily fecundability and the width and location of the associated fertile interval in the menstrual cycle is of interest to both the biologist and the demographer. For the purpose of fertility regulation, the information is essential to those couples attempting to avoid pregnancy and those trying to achieve this end through appropriate timing of intercourse. The need for a large menstrual cycle data base, including a high number of conception cycles, for the purpose of clarifying various points of interest for basic knowledge and applications, has been repeatedly emphasised [Schwartz, MacDonald, and Heuchel 1980, James 1981, Potter and Millman 1986, Royston 1991, Royston and Ferreira 1999].

This paper introduces the results of an exercise performed in this direction with the co-operative collaboration of a group of organised centres giving advice to subjects interested in learning about the fertile phase of the woman and the use of a Natural Family Planning method to avoid or achieve pregnancies. To reach the planned target number of pregnancies (about 500) with a prospective design in a reasonable amount of time, the participation of several centres was necessary. In the following is given a summary description of the common protocol adopted and of the whole study design. We also describe the characteristics of the study subjects and centres and present preliminary analytical results. These results give special attention to covariates linked with the magnitude and pattern in the daily conception probabilities. They are compared with previous estimates from the literature. Mention is also made on ongoing lines of research opened by the available database.

2. Materials and Methods

2.1 Study Design and Population

The investigation was planned as a prospective cohort study conducted to determine the daily probability of conception among healthy subjects. The research protocol was reviewed and approved by the Institutional Review Boards of Fondazione Lanza (Padua, Italy) and Georgetown University (Washington D.C., U.S.A.). The study was co-ordinated from the Department of Statistical Sciences of the University of Padua (Padua, Italy).

From 1992 through 1996, 782 women were recruited with the collaboration of seven European centres (Milan, Verona, Lugano, Düsseldorf, Paris, London and Brussels) providing services on fertility awareness and natural family planning. The entry criteria for the subjects were: women experienced in use of a Natural Family Planning method; married or in a stable relationship; between 18th and 40th birthday at admission; having at least had one menses after cessation of breastfeeding or after delivery; not currently taking hormonal medication or drugs affecting fertility. Neither partner could be permanently infertile and both had to be free from any illness that might cause sub-fertility, e. g., endocrine disorders. It was also required that couples did not have the habit of mixing incidences of unprotected and protected intercourse. Women were excluded if any one of the previous criteria was not fulfilled.

Data from an additional 99 subjects were also included retrospectively in view of their relevance to the aims of the study. These data came from a prospective investigation carried out in Auckland, New Zealand, in 1979-85 into the relationship between the interval from intercourse to fertilisation and the sex of the baby conceived. In this study recruitment was made from couples of proven fertility who were contemplating a further pregnancy. For the purpose of timing intercourse, these couples were instructed on how to recognise the fertile period of the menstrual cycle and anticipate ovulation from changes in cervical mucus. The woman partner also recorded her basal body temperature each day. The study design restricted the couples to only one act of intercourse during the fertile phase of the cycle [France et al 1984, France et al 1992]. This requirement, not respected in a few instances, was the probable cause of subjects frequently dropping out of the study if they had not achieved a pregnancy after 3-4 cycles of trying. The resulting short observational period of sexually active non-conception cycles is a plausible source of positive bias in the estimate of the level of daily fecundability in the present study. Therefore, while the Auckland data is of significant value to other aspects of the study, only results from the seven European centres have been used in determining daily probabilities of conception.

A description of the centres, with the names of the local principal investigators, is given in [Note 1].

2.2 Data Collection

In each centre the local principal investigator instructed selected natural family planning teachers about the purpose and the requirements of the study. After completing the instruction phase, the teachers screened and selected the subjects for admission into the study. A woman satisfying all the inclusion criteria was enrolled only after having given written informed consent. In order to ensure complete subject anonymity and confidentiality, each subject was assigned a study number and only the teacher maintained a personal relationship with the subject. The mutual trust established in this relationship was essential to maintaining the collection of quality reliable data of a sensitive personal nature, which encompassed sexual behaviour.

All the charts were periodically sent to the Department of Statistics at the University of Padua, where uniform evaluation for all cases of the recorded basal body temperature (BBT), taken on awakening in the morning before engaging in any activity, was conducted. Coding of mucus typology, in accordance with agreed common rules, was done in the local centres.

2.3 Study Factors

At entry into the study, the following information was collected: the month and year of birth of the woman and of her partner; the number of previous pregnancies, if any; the date of her last delivery (or miscarriage) and of the end of breastfeeding, if relevant; the date of last oral contraceptive pill taken, if any. Subsequently, after the collection of data had begun, it was decided to add the date of marriage for married couples and the sex of any baby conceived and born during the period of the study. This latter information is available for a large proportion of subjects.

In each menstrual cycle the woman was asked to record on a chart the days of her period and of any disturbance such as illness, broken sleep. She was asked to also record her basal body temperature on the chart for as many days as necessary to determine a clear post-ovulatory rise. She was further asked to observe and chart her cervical mucus symptoms daily during the cycle, and to record every episode of coitus, with specification of whether it was unprotected or protected (barrier methods, withdrawal, ...). Cycles in which even a single act of protected intercourse or of simple genital contact occurred were excluded from the analysis. The reliability of the information recorded of acts of intercourse was checked by the teacher in discussion with subjects at the end of each cycle. The importance of continuing to keep the record chart when subjects were trying to conceive a pregnancy was emphasised.

Charts were regularly collected by the teacher concerned. Following review at the local centre and scoring of the cervical mucus symptoms according to the common rules agreed for the study (Table 1), the charts were sent to the co-ordinating investigators in Padua for processing and entry into the data base [Note 2].

2.4 Definitions

A menstrual cycle was characteristically defined as the interval in days from the beginning of one period of vaginal bleeding until the commencement of the next, where day 1 was the first day of fresh red bleeding, excluding any preceding days with spotting.

The "three over six rule" was used to determine the BBT shift, defined as follows: the first time in the cycle that three temperatures were recorded all of which were above the level of the immediately preceding six daily temperature recordings. Such a rule has been shown to perform well in predicting the start of the infertile period following ovulation [Marshall 1968]. Exceptions to the rule were permitted: a) if there was one "spike" temperature among the six at the lower level (a spike temperature was defined as a temperature which was 0.2 centigrades or more above both its immediate neighbouring temperatures); b) or, in a cycle in which the impact of illness or other disturbances could be discounted, if there were at least six lower temperatures recorded before the upward shift. In analyses in which the BBT rise was used as a conventional indicator for timing ovulation, the last day of lower temperatures was designated as day 0, the "BBT reference day", to which all preceding and following days were scaled according to their distance by integer numbers.

The cervical mucus peak day was defined as the last day with best quality mucus, in a specific cycle of the woman, by sensation or appearance, known retrospectively. This peak day was taken as "Mucus reference day" and identified as day 0.

A conception was assumed in the presence of a pregnancy going on at 60 days from the onset of the last menses or when before that term a miscarriage was clinically detected.

2.5 Statistical Analysis

All the following statistical analyses, performed in the Department of Statistical Sciences, at the University of Padua, were limited to cycles in which ovulation occurred, or at least appeared to occur, and BBT reference day and/or mucus reference day was identified.

We first chose the window of potential fertility to be the series of days relative to the identified day of ovulation such that a cycle without intercourse during these days never resulted in a pregnancy. Daily estimates of probability of conception (a simple division: day by day, number of pregnancies/number of acts of intercourse) were then calculated using cycles with only one intercourse during the putative window. Since the act responsible for conception was unknown in cycles with more than one act of intercourse in the fertile interval, a more sophisticated procedure was needed to estimate globally the daily fecundability in the general case with one or more than one act of intercourse in the window. For this purpose the Schwartz model [Schwartz, MacDonald, and Heuchel 1980] (see [2.5.1]), which is an extension of the one suggested by Barrett and Marshall [Barrett and Marshall 1969], was used. For each cycle, the

probability of no conception is the probability the cycle is not viable plus the probability the cycle is viable and none of the intercourse acts result in successful fertilisation and survival to detection.

Inference was based on the likelihood: (i) parameter estimates were obtained by maximum likelihood, (ii) confidence intervals were then computed for each parameter of interest using the profile log-likelihood [Clayton and Hills 1993] and (iii) likelihood ratio tests were used to assess the significance of selected covariates.

Descriptive analysis was performed using SAS (see http://www.sas.com). R (http://www.r-project.org) was used to fit the Schwartz et al. model to the data. Functions and scripts are available upon request from the authors.

2.5.1 The Schwartz Model [Schwartz, MacDonald, and Heuchel 1980]

For each cycle, the observed outcome (conception/non conception) can be modelled as a Bernoulli random variable with parameter (the probability of success, i.e., the fecundability) that depends on the number and timing of the intercourse events.

Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] write fecundability as the product of three probabilities:

$$\text{fecundability} = P = P_0 \cdot P_f \cdot P_v$$

where $P_0 = \text{pr}(\text{that a fertilizable ovule is produced})$

$P_f = \text{pr}(\text{that the ovule is fertilized} \mid \text{fertilizable ovule})$

$P_v = \text{pr}(\text{that the conceptus stays alive for at least six weeks} \mid \text{fertilized ovule})$

To link P_f to the locations of the acts of intercourse, Schwartz et al. assume, following Barrett and Marshall [Barrett and Marshall 1969], that (i) different intercourse events have independent effects on the outcome and (ii) the probability of conception following intercourse only on day i (defined relative to the reference day [2.4]), $P_{f,i}$ say, is constant between couples and cycles.

Then, fecundability can be written as

$$P = k \cdot P_f = k \cdot \left[1 - \prod_i \left(1 - P_{f,i}\right)^{x_i}\right]$$

where k, called the cycle viability, denotes the product $P_0 \cdot P_v$, while

$$x_i = \begin{cases} 1 & \text{presence of intercourse in the i th day} \\ 0 & \text{otherwise} \end{cases}$$

3. Results

3.1 Overview of the Sample

The characteristics of the 881 subjects enrolled in the various centres and of the 7017 considered cycles, with their outcomes, are summarised in Tables 2, 3, and 4. The number of subjects and contributed cycles varied markedly between centres and consequently, in order to obtain meaningful fecundability patterns from the analysis, some aggregation of data was made. In most analyses the data from Auckland were kept separate from those of the European centres owing to their specific features mentioned in [2.1] having an impact on the level of fecundability.

The average age of women in the study population was close to 29 years and was relatively similar at each centre (Table 2). The proportions of women of proven fertility and of those with past use of hormonal contraception are, however, very different among the centres. For the European centres overall, the percentage of women with at least one previous pregnancy was only 44.6% (range for centres: 30.8 - 73.1) while only 30.1% (range for centres: 11.4 - 56.2) had ever used hormonal contraception in the past (Table 2).

For these same centres, Table 3 underlines the high frequency of cases (96.4%) in which, when enough information was available, the described procedure allowed the BBT shift to be determined. However, when at least some information on temperature was recorded, in further 6.1% of the cycles the reference day could not be identified due to missing information on critical days, and in 1.6% due to disturbing illness. The proportion of cycles with determination – in similar conditions- of the mucus reference day is a little lower (94.1), owing to the particularly low percentage of the Paris subgroup. At that centre, in local usage, mucus symptoms are taken into consideration mainly for identification of the beginning of the "fertile" phase. The 575 detected pregnancies listed according to centres in Table 3 include both those continuing at 60 days from the onset of the last menses and the 49 clinically recognised miscarriages of the same period (also listed).

The figures of Table 4 -5591 cycles with BBT reference day (Table 4a) and 5928 with mucus reference day (Table 4b)- are linked with a conventional determination of the post-ovulatory phases starting after the respective reference days. They give an impression of a remarkable homogeneity between centres. The length of the phase after the peak mucus day in the various centres parallels similar results obtained in the WHO [World Health Organization 1983] study on the ovulation method. As expected, the length of the preovulatory phase shows a relative variability higher than that of the postovulatory one: e.g., for the European aggregate the coefficient of variation (4.74/16.7) is 25.7% in the first vs. 16.2% in the second.

It has to be noted that the two samples - with information on BBT and/or mucus - coincide in a sizeable proportion of cycles (5390 in the combined European group, 232 in Auckland: in the two sets of data both surrogate markers of ovulation were determined in about 80% of the cycles). On average, the peak mucus symptom occurred 0.31 days (S.d. 1.82) before the last low

temperature day in the European group (0.30 with S.d. 1.83 when the Auckland data were included).

The database can also be used in various forms to study the behaviour of the subjects. Table 5, showing the decline in the frequency of intercourse with the increasing age of each of the partners, provides an example. Three points have to be considered: the number of men above 40 is rather small; in conception cycles only acts of intercourse up to the 29th day of the cycle were counted; for obvious reasons, the data are for European centres only. The trend with age, evaluated through the arithmetic average (preferred to the median for sake of better evidence), and the higher coefficient of variation in non-conception cycles (61.3% vs. 49.7%), both support the reliability of the data collected. The small variations between the male and the female findings reflect differences in the number of subjects in the various classes and on the whole. For female partners, over all age groups, the median number of recorded acts of intercourse (10th, 90th percentiles) is equal to 6 days (3,11) in the conception cycles and to 4 (1,8) in the non-conception cycles.

Table 6 lists the distribution of 5390 cycles according to the interval in days between the two markers of ovulation (BBT reference day minus mucus reference day). We know already - from [3.1] - the value of the average distance between those days. There is some translation between the two reference terms, which -though small - can influence the comparative distributions of cycles, and of intercourse episodes and pregnancies allocated to the various days of the respective fecundability window. In the majority (62.4%) of the cycles the two markers are within ± one day and the difference is greater than ± two days in 17% of the cycles. This suggests that estimates of day-specific pregnancy probabilities should not depend greatly on which marker is used for ovulation. However, we cannot rule out possible overestimation of the fertile interval relative to BBT or mucus reference day compared with the width of the fertile interval relative to the true day of ovulation. Although efforts were made to rule out errors in documentation of BBT or cervical mucus, measurement errors can result due to unavoidable biological variability. In future work, such measurement errors could be assessed and corrected using recently developed statistical methodology [Dunson and Weinberg 2000, Dunson et al in press].

3.2 Fertility Windows: Direct Estimates of Fecundability

In order to find windows of fertility - around the BBT or the mucus reference day - to be used for estimates of daily fecundability, an exploratory analysis was made, changing width and location of chosen windows. For each reference marker, it was found that, when no intercourse episodes were ascertained in a 12-day window, no pregnancy was recorded. Eight among the 12 days preceded the day 0 and three came afterwards.

Then, direct estimates of daily fecundability were computed inside these windows. In this initial determination, only cycles with a single act of intercourse in a window were selected. The ratio of instances in which the acts of one day resulted in conception to the total number of acts of intercourse of the same day gave, for that day, an estimate of the probability of conception. The results are presented in Table 7 for the combined European centres (top section) and with inclusion of Auckland for all centres (bottom section). The differences in the number of cycles between the bottom and the top grouping give the contribution from Auckland. The two sets of probabilities are very different, particularly when the impact of the Auckland data, in terms of number of conception cycles, is relevant: direct estimates obtained for this site are on the average about double those of the European ones. It is worth mentioning that no one of the almost 350 intercourse episodes of the third day of the high BBT gave rise to a conception. And also that Auckland conforms to the other centres concerning the width of the window, which might be shorter, even when due account is taken of the smaller sample size.

A similar exercise was performed, with data only from European centres, with the aim of obtaining more precise fecundability estimates by increasing the number of contributing cycles through use of a smaller window, in which the probability of having single intercourse episodes is increased. Cycles, however, were eliminated from consideration in which, while only a single act of intercourse occurred in the shorter window, conception might have been due (though certainly with a small probability) not to that coital act but to intercourse episodes falling outside the window. From this point of view, were considered relevant, for cycles having intercourse on day -6, the three days -9, -8, -7, reduced to two (-8, -7) for cycles with intercourse on day -5, and to one (-7) in cycles with intercourse on day -4. Similarly, were excluded from the analysis cycles with intercourse on day +2. The elaboration was extended to evaluate a parallel window around the mucus reference day. The results for both analyses are shown in Table 8. In absolute terms, the main differences between the two sets of probability are observed on days -3 and 0. Considering - besides random errors and the small shift in BBT versus mucus - that the two aggregates of cycles are different, the estimates of fecundability, daily and total, appear in good agreement. Worthy of attention is the finding that the peak mucus day is not the one with maximum fecundability. In each aggregate, the four days preceding the reference day are the most relevant for cycle fecundability.

3.3 Estimates through a Model

In the presence of multiple acts of intercourse during the fertile interval of a cycle, the probability of conception due to a single act on any day cannot be estimated directly. One has to make use of a model whose computed coefficients may lead to an evaluation of daily fecundability. For this purpose, in the following, estimates of day by day conception probabilities are obtained through the application of the Schwartz model [Schwartz, MacDonald,

and Heuchel 1980], summarised in [2.5.1]. This model has been repeatedly used in the literature, and by that it allows comparisons with other experiences.

The model estimates of daily fecundability for the European subjects are presented in Table 9, with confidence intervals obtained through the profile maximum likelihood [Clayton and Hills 1993], at the 90% level. The chosen windows are those already seen. The two sets of data have a different composition, but once again they underline in both cases the significance of higher rates in the four days preceding the respective reference day.

In Figure 1, the daily estimates relative to each of the two markers of ovulation are presented. These estimates are based on the 5390 cycles from the European centres for which both reference days are available. There is a total of only 386 pregnancies, since for 48 there is information only on the peak mucus day, for 49 only on BBT shift, and nothing in 4 instances. The given confidence intervals are at the 90% level. Several points may be mentioned: a) in the two sets of estimates, though the total number of cycles is the same, the number of those with at least one intercourse episode in the window differs: 2917 for BBT and 2843 for mucus, respectively. This difference will have an effect, though small, on the respective areas under the curve; b) one has to remember the mentioned average distance between the two reference days and its possible effects (see para 7 of [3.1]); c) the estimates based on the mucus symptom conform less well to a bell shaped pattern as observed with the BBT window; d) the dip at day -3 found through the mucus symptom repeats what seen in the data set of Table 9 and also in the direct estimates of Table 8: a point deserving further elaboration.

It appears that the BBT reference day may be a slightly better (i.e. less error prone) marker of ovulation day, since the estimates, compared with those around the mucus reference day, are higher on the days of peak fertility (i.e. days -3 to -1) and lower on the days towards the edge of the window.

In Table 10 the results for the 12 days BBT window are compared with fecundability estimates reported from five other similar studies. A few notes will clarify the limits of these comparisons. The discrepancies between the different sets of probabilities can be attributed - apart from random errors- to different characteristics of the subjects, to distinct procedures followed in determining the ovulation reference day and to the inclusion or exclusion of early miscarriage in the counted pregnancies. The probabilities reported by Schwartz et al. [Schwartz et al 1979] are direct estimates from single donor artificial inseminations per cycle by donors. The data by Weinberg et al. [Weinberg et al 1998] and by Wilcox et al. [Wilcox, Weinberg, and Baird 1998] come from recruitment from the general population of subjects wanting to achieve a pregnancy. In the other two studies, the information was collected in centres providing services on fertility awareness and natural fertility regulation. Weinberg et al [Weinberg et al 1998] were able to include through assay of hCG very early pregnancies losses, otherwise undetected by clinical diagnoses. In the same set of pregnancies, Wilcox et al. [Wilcox, Weinberg, and Baird 1998] considered only those clinically diagnosed, that is events more similar to those considered in the present aggregate of European centres. In the other studies there were no important

differences in the recording of pregnancies. In conception cycles with multiple acts of intercourse in the "fertile" window, Bremme [Bremme 1991] chose to assign pregnancy to the intercourse which occurred closest in time prior to or coinciding with the presumed day of "ovulation": a procedure leading to a bias which increased fecundability rates as the "ovulation" day was approached. For the probabilities computed in Weinberg et al [Weinberg et al 1998] and in Wilcox et al. [Wilcox, Weinberg, and Baird 1998] ovulation day (i.e. day 0) was identified using the decline in the ratio of oestrogen to progesterone metabolites in the urine that accompanies luteinization of the ovarian follicle [Baird et al 1991]. This steroid based marker should be less error-prone than markers on BBT or mucus, but should not deviate systematically from the last day of low temperature used in the other studies, as in the present data base. Apart from Bremme and Schwartz et al [Schwartz et al 1979], the other four sets of estimates were based on the Schwartz model [2.5.1].

Figure 2 shows a graphical comparison of the pattern of conception probabilities in the BBT window for four subgroups (centres or combinations of centres) and for the whole European experience. The results for the Auckland subjects clearly differ from those of the other instances. The other three subgroups consisted of the Verona centre, Milan aggregated with Lugano because of similarity of NFP teaching content and method, and the four remaining European centres combined because of their small sample sizes. The homogeneity of the fecundability data between the three European subsets is striking. The maximum likelihood ratio test of significance of the differences between the three European subsets gives $p>0.10$. The merging of their records in a unique European group appears reasonable: this will form the basis of all subsequent analyses on the level of fecundability

Figures 3, 4 and 5 focus on the link between three covariates pertaining to the female subjects and fecundability in the window around the BBT reference day. The covariates evaluated are: the reproductive history of the woman, by comparing subjects with and without a previous pregnancy (Figure 3); the woman's age, by dividing the subjects into three age groups, 18-24 yrs (103 subjects), 25-34 yrs (596), and 35-39yrs (83; Figure 4); and past use or non use of oral contraception (Figure 5). The difference in the level of fecundability of the women of proven fertility versus the unproven group is very significant ($p = 0.014$). In the group with unproven fertility, though the subjects obviously believed they were fertile, their number would include some with undiagnosed infertility or sub-fertility as in the general population. Furthermore, at least in one Italian centre, subjects may have been included in the study who were seeking help in achieving a pregnancy after a prolonged experience of failure. No marked differences in fecundability rates were observed in the three age groups ($p>0.10$), though the sample sizes in the younger and older groups are relatively small. When the subjects were divided into those below and those above the median age (29 years), again no significant difference in fecundability was found between the two groups ($p>0.10$, data not shown). Similarly, no significant differences ($p>0.10$) are seen in the daily fecundability when comparisons are made between past use or no previous use of oral contraception. It should be

noted, however, that the number of women having used this method of contraception in the three cycles preceding their entry into the study is extremely low (3.0%).

Two further results pertaining to the cycles are presented in Figures 6 and 7. Figure 6 is based on the data of Table 6. The whole set of cycles is divided into three groups according to the time difference between the BBT reference day and the peak mucus day: group 1, negative difference (1569 cycles, 29.1% of the total); group 2, difference equal to 0 and 1 days (2553, 47.4%); group 3, greater than 1 day (1268, 23.5%). For each of the three derived sub-sets the Figure shows the pattern of estimated daily conception probabilities. Attention is drawn to the sub-set in which the two reference points (almost) coincide, and therefore should support each other as giving a rather good approximate indication on the time of ovulation. The pattern of conception probabilities appears very concentrated, falling after a continuous rise extending over five days, with a maximum at day –2, approaching zero at both extremes (see also Wilcox et al. [Wilcox, Weinberg, and Baird 1998]). The pattern is somewhat similar in group 3, though more elevated at beginning of the ascending part and then falling abruptly on day zero, remaining then at this level. When the peak mucus day occurs after the BBT reference day (group 1) the probability pattern is very irregular with two maxima (on day -3 and day 0). The difference between the three sets of probabilities is very significant ($p=0.020$).

Figure 7 illustrates the pattern of daily fecundability for two different subsets of cycles, one with the window around the BBT shift (3175 cycles with at least one intercourse in the window, 434 pregnancies) and the other with the window around the mucus reference day (3265 cycles, 435 pregnancies). The two subsets are each further divided according to the length of the conventional follicular phase of the cycles, <16 days and > = 16 days The very different shape of the two derived patterns of fecundability is highly significant ($p=0.003$ for BBT, $p<0.001$ for mucus). The differences in probability levels on, say, day –4 depending on the said length is very strong. Evidently the distance -4 does not have the same meaning for all cycles: as does the distance at day zero, though with inverse relationship in the probabilities of the two subsets. The evidence is the same for both BBT and mucus which tends to exclude systematic errors in the identification of the reference days as an explanation. There is a biological foundation for such a result or does this serve as a hint to consider more stable the positioning of ovulation in the cycle and more variable that of the conventional surrogate indicators?

4. Discussion

The startling variety of suggestions concerning the width of the "fertile window" found in the literature depends in part from conceptual approaches adopted. To try and measure the window summing lifetime of sperm and ovum -less the time needed for capacitation of spermatozoa -is a deductive theoretical solution. But when, instead of a single cycle, a mixture of cycles of a group of women is considered, due account has to be taken of the biological variability of both patterns and its interaction. When trying to make evaluations starting from aggregates of distinct empirical experiences, one should be sure that the single cases record real facts uniformly and homogeneously, without the impact of confounding factors. According to Potter and Millmann [Potter and Millman 1985], the lines of research followed to clarify the point can be grouped into two categories. In the first one, assumptions are made on mean fecundability and average coital pattern: a chosen model allows us to estimate the length of the fertile period assuring compatibility between the two. In the second, starting from estimated daily probabilities, given a certain coital pattern, the fecundability in a cycle is derived.

The procedure followed in this exercise falls into this second class. That is, it starts from and deals with aggregations of distinct ascertained facts. One aspect of the documentation that has been collected needs to be stressed here: that is, its reliability about type and timing of what is essential for the study of fecundability, the acts of intercourse. This has been assured by the long experience of the co-operating centres, an agreed rigorous protocol, the follow up of the ongoing work through periodical meetings of the Principal Investigators, the scrupulous screening of the forms arriving at the co-ordinating centre.

At the same time, the main weakness of the information has to be underlined: the reliance on the surrogate indicators of the true day of ovulation, the BBT shift and the peak mucus day. The distribution of deviations between these markers and the true ovulation day is poorly known (see, e.g. [Hilgers, Abraham, and Cavanagh 1978, Hilgers and Bailey 1980, France 1982, Guida et al 1999]). Several recent studies have obtained estimates of error in BBT reference day. There have been small validation studies and Dunson et al. [Dunson et al 1999] present estimates. These studies suggest that most cycles have errors of less than ± one day. A major challenge is to try to obtain correct measures of daily fecundability, possibly using the methods of Dunson and Weinberg [Dunson and Weinberg 2000] and Dunson et al. [Dunson et al in press]. Furthermore, while ovulation is practically instantaneous, we have only information on the level of days.

The Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] model (see [2.5.1]) chosen has its merits: it rests on appealing biological hypotheses, and in general fits well the data. But it has weaknesses: it is based on rather simplistic assumptions; with high frequency of intercourse it tends to underestimate observed fecundability; the parameter k, supposed to measure the so-called cycle viability, is not independent from the pattern of intercourse episodes. But it is not the place, here, to enter into a thorough discussion of comparative evaluation of advantages and

disadvantages of different proposed or conceivable models, or of other approaches to the desired estimation.

These words of caution do not detract significance for applications from the main results of the study in the area of fertility regulation. Couples attempting pregnancy should maximise their intercourse frequency during the four days preceding the first upward shift of the basal body temperature or the peak mucus day. In both distinct sets of cycles the maximum level of conception probabilities is achieved in the second day before the reference point: 0.255 in the window around BBT reference day and 0.203 in the other case. Couples wanting to avoid pregnancy are informed that the unsafe period might be extended up to 11-12 days. The computed confidence intervals may help to qualify the situation obtaining at the two extremes of the window, where the probabilities of conception are very low. In both sets, eight days before the reference point the estimated probability is 0.003, which means, approximately, a pregnancy every 26 years: but the computed upper confidence limits reach 0.011. Obviously, these conclusions are drawn from *a posteriori* observation, but concerning the determination of the beginning of the pre-menstrual infertile phase they provide sufficient information. For other purposes, needing day to day decisions, apart from some observations currently possible - as a first evidence of the mucus symptom -, it would be advantageous to be able to make reliable forecasts. For this sake, an improvement of usual calendar methods through a sequential procedure using updated accumulated observations made on preceding cycles might prove useful.

The results obtained are of interest also from a demographic point of view. Contraception has an obvious impact as a confounding factor on the link between so-called natural and actual fertility of a population. The said results make clear how behaviour together with physiology has an influence on natural fertility. What matters is not only frequency of coitions, but also their allocation to the different days of the fertile interval. The maximum daily fecundability estimated in the BBT window is .255 (Table 9) which corresponds to an average number of 3.92 cycles needed for obtaining a pregnancy, while after one year (roughly 13 cycles) 2.2% subjects remain without success. Couples with at least three acts of intercourse in the same window –roughly representing those attempting a pregnancy- reach a proportion of .227 conception cycles on the whole. This corresponds to 4.41 cycles for a pregnancy and 3.5% of failures in a year.

After the elaboration for the whole data set, some covariates are taken into consideration, one by one: centres, reproductive history and age of the women, and previous use of oral contraception. Homogeneity was observed among three sets of European populations both in pattern and level of conception probabilities and in the extension of the fertile window. Auckland shows the same pattern but a significantly higher level of probabilities. Similar results are reached in the other elaboration on the European set, with a clear difference in the level of daily fecundability only according to previous reproductive experience. Attention should be drawn, however, on the upper age limit of 40 years for the women, the lack of standardisation with respect to the reproductive history of the woman and the decline of k with increasing age. The

interrelations between covariates -for instance between age and reproductive history of the women- show that for the distinct evaluation of the impact of various factors, a multivariate analysis approach is needed. A consideration of heterogeneity between units due to unobservable phenomena has to be added to this. The study design is rather complex, hierarchical and multilevel. Considering the women subjects, there are days in a cycle, cycles in a woman, women in a centre, various centres. At each level there is involvement of specific covariates and there is unobservable heterogeneity between the units. Furthermore, there is a confounding factor, the age of the partner.

If one wants - particularly in view of more efficient applications in the field of fertility regulation - to try to make clusterization of subjects, the results by cycle shown in Figures 6 and 7 suggest that longitudinal analyses of consecutive cycles within women are needed to characterise them. Also, longitudinal analysis of cycles might prove useful in clarifying the impact of physiology and behaviour on the outcomes: a rather intriguing area of study since at every step the event -number and allocation of acts of intercourse- may change.

These examples show that the database presented in this paper offers possibilities of investigation along several lines of research.

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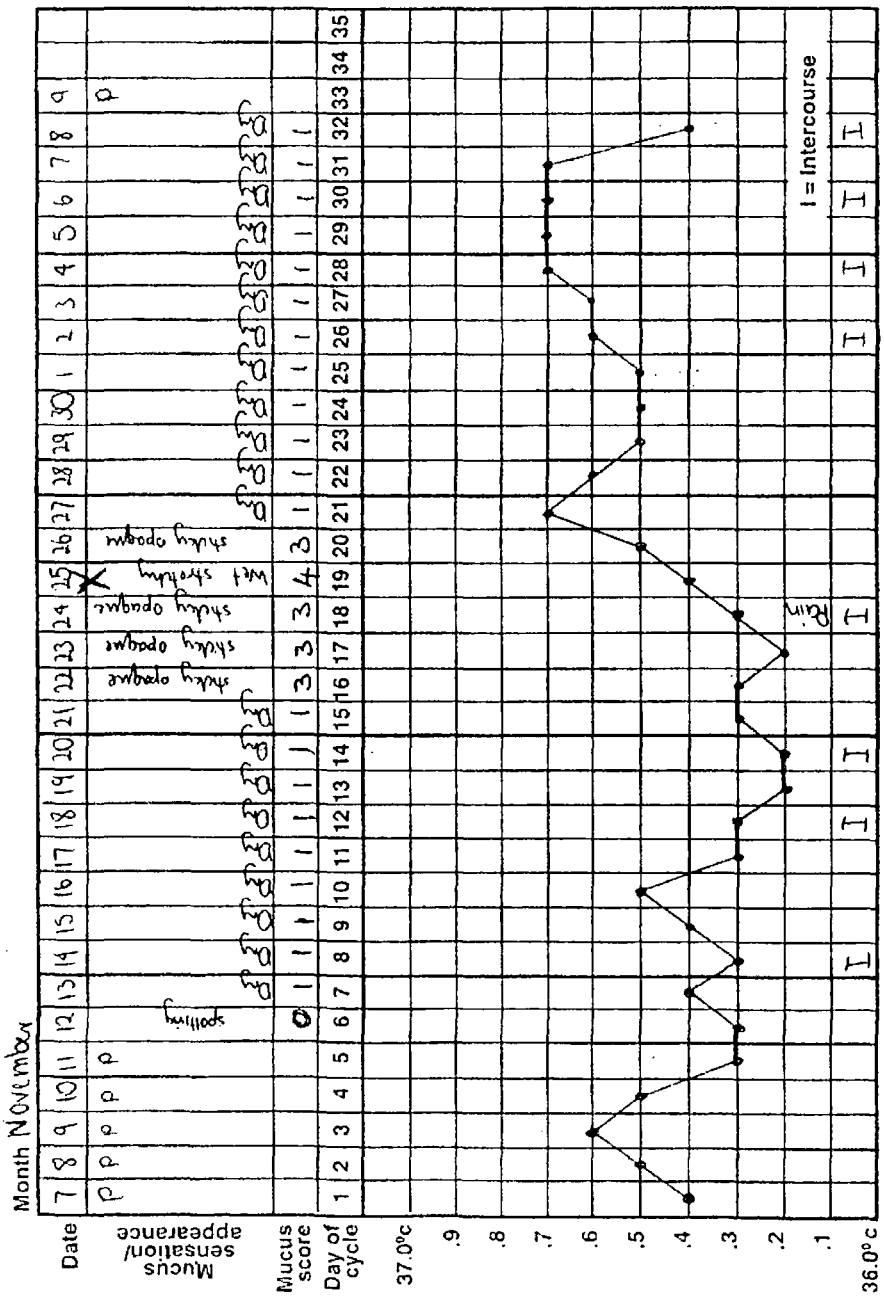
Notes

1. The Study Group Investigators were: Michele Barbato, M.D., Centro Ambrosiano Metodi Naturali, Milan, Italy, Priscilla Coppieters, M.D., Fédération Francophone pour le Planning Familial Naturel, Couple-Amour-Fécondité, Brussels, Belgium, John France, PhD., DSc., Research Center in Reproductive Medicine, Department of Obstetrics and Gynaecology, University of Auckland School of Medicine, Auckland, New Zealand, Sandro Girotto, M.D., Istituto per l'Educazione alla Sessualità e alla Fertilità (INER – Verona), Verona, Italy, Christian Gnoth, M.D., Natürliche Familien Planung, Frauenklinik, University of Düsseldorf, Germany, Jane Knight, R.N., Fertility UK, London, United Kingdom, Lucia Rovelli, Centro Metodi Naturali di Lugano, Lugano, Switzerland, Cathérine Renard Denis, Centre de Liaison des Equipes de Recherche, Paris, France, and General Coordinators: Bernardo Colombo, Emer. Prof., and Guido Masarotto, Prof., Dipartimento di Scienze Statistiche, Università degli Studi, Padua, Italy.
2. An example of a menstrual cycle record chart received in the coordinating centre of Padua. The cross on the date indicates the peak mucus day.

Subject code : 12.010.0142 001



References

Baird DD, Weinberg CR, Wilcox AJ, McConnaughy DR. Using the ratio of urinary oestrogen and progesterone metabolites to estimate day of ovulation. *Statistics in Medic.,* 1991, 10, 2: 255-266.

Barrett JC. Fecundability and coital frequency. *Popul. Studies,* 1971, 25, 2: 309-313.

Barrett JC, Marshall J. The risk of Conception on Different Days of the Menstrual Cycle, *Popul. Studies*, 1969, 23, 3: 455-461.

Bremme J. Sexualverhalten und Konzeptionswahrscheinlïchkeit (Auswertung einer prospektiven Studie zur Natürlichen Familienplanung), *Thesis*, 1991, Med. Fakultät der Heinrich. – Heine – Universität, Düsseldorf

Bongaarts J, Potter LG. Fertility, Biology and Behavior, 1983, New York, Academic Press, 35-38.

Clayton D, Hills M. Statistical Models in Epidemiology, 1993, Oxford, Oxford University Press: 124-128.

Dunson DB, Baird DD, Wilcox AJ, Weinberg CR, Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation, *Human Reproduction*, 1999, 14, 7 : 1835-1839.

Dunson DB, Weinberg CR. Modeling Human Fertility in the Presence of Measurement Error, *Biometrics*, 2000, 56, 1: 288-292.

Dunson DB, Weinberg CR, Baird DD, Kesner JS, Wilcox AJ. Assessing human fertility using several markers of ovulation, *Statistics in Medic.*, in press.

France JT. The Detection of Ovulation for Fertility and Infertility. *Recent Advances in Obstetrics and Gynaecology.* Ed J Bonnar, 1982, No 14: 215-239.

France J, Graham FM, Gosling L, Hair P. A prospective study of the preselection of sex of offspring by timing intercourse relative to ovulation. *Fertility and Sterility,* 1984, 41, 6: 894-900.

France J, Graham FM, Gosling L, Hair P, Knox BS. Characteristics of natural conceptual cycles occurring in a prospective study of sex preselection: Fertility awareness symptoms, normal levels, sperm survival, and pregnancy outcome. *Intern. J. of Fert.,* 1992, 37, 4: 244-255.

Gini C. Prime ricerche sulla "fecondabilità" della donna, *Atti reale Istituto Veneto di Scienze Lettere ed Arti*, 1924, 83, 2: 315-344.

Gini C. Premières recherches sur la fécondabilité de la femme, *Proc. of the Intern. Mathem. Congress, Toronto, Aug. 11-16, 1924, Vol. II,* Fields JC Ed., 1928, Toronto, The Univ. of Toronto Press: 889-892.

Glass D., Grebenik E. *The Trend and Pattern of Fertility in Great Britain*, Papers of the Royal Commission on Population, 1954, 6, 1: 255.

Glasser JH, Lachenbruch PA. Observations on the Relationship beetween Frequency and Timing of Intercourse and the Probability of Conception, *Popul. Studies,* 1968, 22, 3: 399-407.

Guida M, Tommaselli GA, Palomba S, Pellicano M, Moccia G, Di Carlo C, Nappi C, Efficacy of methods for determining ovulation in a natural family planning program, *Fertility and Sterility,* 1999, 72, 5: 900-904.

Hilgers TW, Abraham GE, Cavanagh D. Natural family planning. I. The peak symptom and estimated time of ovulation, *Obstetrics and Gynecology,* 1978, 52, 5: 575-582.

Hilgers TW, Bailey AJ, Natural family planning. II. Basal body temperature and estimated time of ovulation, *Obstetrics and Gynecology,* 1980, 55, 3: 333-339

James WH. Estimates of Fecundability, *Popul. Studies,* 1963, 17, 1: 57-65.

James WH. Distributions of Coital Rates and of Fecundability, *Social Biology,* 1981, 28, 3-4: 334-341.

Lachenbruch PA. Frequency and Timing of Intercourse: Its Relation to the Probability of Conception, *Popul. Studies,* 1967, 21, 1: 23-31.

Loevner DR. Estimation of Risks of Conception and the Fertile Period, *B. A. Thesis*, 1976, Princeton University.

Marshall J. Analyse statistique du moment de la concéptìon en rélation avec l'élévation de la température sur 5013 cycles, *Actes du Congrés Mondial la Population,* Belgrade, 30 Août – 10 Septembre. 1965. *Vol. II: Fécondité, Planification de la famille, Mortalité*, 1967, New York, Nations Unies: 305-307.

Marshall J. A field trial of the basal body-temperature method of regulating births. *The Lancet.* 1968, 2: 810.

Masarotto G, Romualdi C. Probability of conception on different days of the menstrual cycle: an ongoing exercise, *Advanc. in Contrac.*, 1997, 13, 2-3: 105-115.

Miolo L, Colombo B, Marshall J, A data base for biometric research on changes in basal body temperature in the menstrual cycle, *Statistica,* 1993, 53, 4: 563-572.

Potter RG. Length of the fertile period, *Milbank Memor. Fund Quart.* 1961, 39, 1: 132-162.

Potter RG, Millman SR. Fecundability and Frequency of Marital Intercourse: A Critique of Nine Models, *Popul Studies*, 1985, 39, 3: 461-470.

Potter RG, Millman SR. Fecundability and Frequency of Marital Intercourse: New Models Incorporating the Aging of Gametes, *Popul. Studies*, 1986, 40, 1: 159-170.

Royston JP. Basal body Temperature, Ovulation and the Risk of Conception, with special Reference to the Lifetimes of Sperm and Egg, *Biometrics,* 1982, 38, 2: 397-406.

Royston P. Identifying the Fertile Phase of the Human Menstrual Cycle, *Statistics in Medic.*, 1991, 10, 2: 221-240.

Royston P, Ferreira A. A New Approach to Modelling Daily Probability of Conception, *Biometrics,* 1999, 55, 4: 1005-1013.

Schwartz D, Mayaux MJ, Martin-Boyce A, Czyglik F, David G. Donor insemination: conception rate according to cycle day in a series of 821 cycles with a single insemination, *Fertil. Steril.*, 1979, 31, 2: 226-229.

Schwartz D, MacDonald PDM, Heuchel V. Fecundability, coital frequency and the viability of ova, *Popul. Studies,* 1980, 34, 2: 397-400.

Sinai I, Jennings V, Arévalo M. The Two Day Algorithm: A New Algorithm to Identify the Fertile Time of the Menstrual Cycle, *Contraception*, 1999, 60, 2: 65-70.

Tietze C. Probability of conception resulting from a single unprotected coitus, *Fertil. Steril.,* 1960, 11, 5: 485-488.

Trussell J. Natural fertility: measurement and use in fertility models, in *Natural Fertility* (Léridon H, Menken J Eds.), 1979, Liège, Ordina Editions: 31-64.

Trussell J. Conception Probabilities by Cycle Day, *Memorandum,* 1996, Office of Population Research, Princeton University.

Vincent B. Atlas de Courbes Thermiques, 1964, Edition 4, Nantes, Centre de Documentation et d'Information Conjugale : 60.

Vollman RF. Assessment of the fertile and sterile phases of the menstrual cycle *Intern. Rev. of Nat. Fam. Plann.,* 1977, 1, 1: 40-47.

Weinberg CR, Gladen BC, Wilcox AJ. Models Relating the Timing of Intercourse to the Probability of Conception and the Sex of the Baby. *Biometrics*, 1994, 50, 2: 358-367.

Weinberg CR, Wilcox AJ, Baird DD, Gladen BB. The probability of conception as related to the timing of intercourse around ovulation. *Genus*, 1998, 54, 3-4: 129-142.

Wilcox AJ, Weinberg CR, Baird DD, Post-ovulatory ageing of the human oocyte and embryo failure, *Human Reproduction,* 1998, 13, 2: 394-397.

Wood JW. Dynamics of Human Reproduction – Biology, Biometry, Demography, 1994, New York, Aldine de Gruyter: 143-150, 295-305.

World Health Organization. A prospective multicentre trial of the ovulation method of natural family planning. III. Characteristics of the menstrual cycle and of the fertile phase, *Fertil. Steril.*, 1983, 40, 6: 773-778.

World Health Organization. A prospective multicentre study to develop universal immunochemical tests for predicting the fertile period in women, *Intern. J. Fert.,* 1985, 30, 3: 18-30.

Table 1:
Classification and codification of mucus symptoms.*

Code of mucus type	Feeling	Appearance of mucus
0	No information	No information
1	Dry, rough and itchy feeling or nothing felt	Nothing seen, no mucus
2	Damp feeling	Nothing seen, no mucus
3	Damp feeling	Mucus is thick, creamy, whitish, yellowish, not stretchy/elastic, sticky
4	Wet, slippery, smooth feeling	Mucus is transparent, like raw egg white, stretchy/elastic, liquid, watery, reddish (with some blood)

* If there are different mucus observations on one day, the most fertile characteristic of the mucus observed determines the classification.

Table 2:
Characteristics of women and men participating in the exercise.

Centres	No. of women	Age of women Mean (Sd)	Age of men Mean (Sd)	No. of women with at least one past pregnancy (% of women)	No. of women with past use of hormonal contraception (% of women)
Verona	214	28.6 (3.54)	30.7 (4.16)	66 (30.8)	63 (29.4)
Milan	272	28.7 (3.56)	31.3 (4.73)	109 (40.1)	31 (11.4)
Lugano	13	29.3 (4.50)	32.1 (3.99)	5 (38.5)	4 (30.8)
Paris	104	29.3 (4.52)	31.4 (5.42)	76 (73.1)	38 (36.5)
Düsseldorf	105	28.2 (4.48)	30.4 (4.86)	44 (41.9)	59 (56.2)
London	45	31.6 (4.68)	34.0 (4.60)	29 (64.4)	24 (53.3)
Brussels	29	29.7 (4.52)	31.6 (3.78)	20 (69.0)	16 (55.2)
Total European	782	28.9 (4.00)	31.2 (4.70)	349 (44.6)	235 (30.1)
Auckland	99	29.9 (3.13)	32.3 (3.87)	96 (97.0)	34 (34.3)

Table 3:
Characteristics of cycles and their outcomes

Centres	No. of cycles	No. of cycles with identification of BBT reference day (% of cycles*)		Mucus reference day (% of cycles†)		No. of cycles with at least one coition in the window‡	No. of detected pregnancies (% of cycles)		No. of miscarriages (% of pregnancies)	
Verona	1279	1133	(97.9)	1246	(98.3)	827	171	(13.4)	11	(6.4)
Milan	3288	2840	(95.4)	3051	(95.8)	1351	151	(4.6)	20	(13.2)
Lugano	57	56	(98.2)	57	(100)	48	13	(22.8)	0	(0)
Paris	787	680	(95.8)	576	(74.0)	340	63	(8.0)	5	(7.9)
Düsseldorf	654	615	(97.8)	650	(99.4)	257	41	(6.3)	3	(7.3)
London	320	250	(95.8)	272	(96.1)	181	30	(9.4)	5	(16.7)
Brussels	339	286	(99.0)	314	(95.2)	171	18	(5.3)	3	(16.7)
Total European	6724	5860	(96.4)	6166	(94.1)	3175	487	(7.2)	47	(9.7)
Auckland	293	238	(94.8)	285	(97.3)	215	88	(30.0)	2	(2.3)

* The percentage is the proportion of cycles with the identified rise in the BBT over the cycles with enough information on the BBT
† The percentage is the proportion of cycles with the identified peak of the mucus over the cycles with enough information on the mucus
‡ Window around the last day of hypothermia

Table 4:
Characteristics of non conception cycles with identification of reference days.

a) With BBT reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	982	29.0	(5.04)	16.4	(5.01)	12.6	(2.09)
Milan	2711	29.1	(3.89)	16.7	(3.93)	12.4	(2.09)
Lugano	44	27.2	(2.24)	14.7	(2.73)	12.5	(2.19)
Paris	620	29.3	(4.92)	17.1	(4.91)	12.2	(1.08)
Düsseldorf	574	28.3	(3.73)	16.3	(3.68)	12.0	(1.89)
London	224	29.8	(4.68)	17.2	(4.56)	12.5	(2.46)
Brussels	271	28.7	(3.63)	16.3	(3.74)	12.4	(1.94)
Total European	5426	29.0	(4.26)	16.6	(4.26)	12.4	(2.07)
Auckland	165	29.5	(4.37)	16.7	(4.64)	12.8	(2.36)

b) With mucus reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	1084	29.1	5.04	15.6	4.91	13.4	2.22
Milan	2913	29.1	3.95	16.6	3.93	12.5	2.07
Lugano	44	27.2	2.24	14.2	2.48	13.0	2.19
Paris	534	29.2	5.01	16.9	5.12	12.3	2.04
Düsseldorf	610	28.3	3.69	15.9	3.52	12.4	2.01
London	245	29.3	4.29	17.4	4.04	11.9	2.54
Brussels	301	28.6	3.56	15.2	3.68	13.4	2.07
Total European	5731	29.0	4.25	16.3	4.23	12.7	2.16
Auckland	197	29.0	4.16	16.2	4.21	12.8	2.43

* Conventionally: Preovulatory phase = until the last day of hypothermia or, respectively, the peak mucus day, included; Postovulatory phase = the remaining part of the cycle.

Table 5:
Average number of acts of intercourse per cycle (European centres)

Age classes (years)	Intercourse of women in				Intercourse of men* in			
	Conception cycles†		Non conception cycles		Conception cycles†		Non conception cycles	
	Mean	(S.d.)	Mean	(S.d..)	Mean	(S.d.)	Mean	(S.d.)
18-24	7.1	(3.19)	5.2	(3.10)	7.4	(3.86)	5.7	(3.47)
25-29	6.5	(3.08)	4.9	(2.82)	6.6	(3.17)	5.1	(3.08)
30-34	5.5	(3.03)	4.2	(2.73)	6.0	(3.00)	4.3	(2.54)
35-39	5.1	(2.30)	3.7.	(1.96)	5.3	(2.65)	4.0	(2.52)
≥40					5.6	(2.62)	4.2	(2.19)
Total	6.2	(3.08)	4.5	(2.76)				

* There are 34 cycles in which the man's age is missing
† In conception cycles, only the first 29 days since the onset of the menses are taken into consideration.

Table 6:
Distribution of cycles according to the distance between the reference days in 5390 cases in which both days have been identified (European centres).*

Distance in days	Number of Cycles	Percent	Number of pregnancies
-9	1	0.0	0
-8	1	0.0	0
-7	1	0.0	0
-6	10	0.2	0
-5	16	0.3	1
-4	108	2.0	5
-3	203	3.8	15
-2	420	7.8	26
-1	809	15.0	56
0	1434	26.6	97
1	1119	20.8	80
2	692	12.8	58
3	356	6.6	29
4	170	3.2	13
5	33	0.6	4
6	14	0.3	2
7	1	0.0	0
8	1	0.0	0
9	0	0.0	0
10	1	0.0	0
Total	5390	100	386

* The distance is the difference: day of last low BBT minus mucus reference day.

Table 7:
Direct estimation of fecundability in the window [-8,3] around the BBT reference day for the European centres and all the centres.

		Distribution of single acts of intercourse in the window												
	Cycles	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	Total
European centres	Conc. cycles	1	1	4	2	9	8	4	5	2	0	4	0	40
	All cycles	265	151	92	55	40	29	26	25	29	35	85	343	1175
	Ratio	0.004	0.007	0.043	0.036	0.225	0.276	0.154	0.200	0.069	0	0.047	0	0.034
All centres	Conc. cycles	1	1	6	5	13	10	12	13	9	2	5	0	77
	All cycles	269	154	97	67	47	35	37	40	46	54	94	348	1288
	Ratio	0.004	0.006	0.062	0.075	0.277	0.286	0.324	0.325	0.196	0.037	0.053	0	0.060

Table 8:
Direct "adjusted" estimation of fecundability in the window [-6,1] around the reference day (European centres).

Reference		Distribution of single acts of intercourse in the window								
		-6	-5	-4	-3	-2	-1	0	1	Total
BBT	Conc. cycles	3	2	11	12	10	10	4	2	54
	All cycles	90	59	50	45	41	54	59	60	458
	Ratio	0.033	0.034	0.220	0.267	0.244	0.185	0.068	0.033	0.118
Mucus	Conc. cycles	4	4	11	8	10	13	6	6	62
	All cycles	86	71	59	43	42	50	52	80	483
	Ratio	0.047	0.056	0.186	0.186	0.238	0.260	0.115	0.075	0.128

Table 9:
Daily estimates in cycles with one or more acts of intercourse in the windows
(European centres; Schwartz et al. model [see 2.5.1])

	BBT reference day		Mucus reference day	
Intercourse day vs reference day	Probability of conception	Lower-Upper 90% Confidence Interval	Probability of conception	Lower-Upper 90% Confidence Interval
		L U		L U
-8	0.003	0.000 - 0.011	0.003	0.000 - 0.011
-7	0.014	0.003 - 0.035	0.000	0.000 - 0.004
-6	0.027	0.013 - 0.049	0.045	0.026 - 0.071
-5	0.068	0.037 - 0.108	0.078	0.046 - 0.118
-4	0.176	0.124 - 0.236	0.181	0.131 - 0.238
-3	0.237	0.179 - 0.277	0.114	0.068 - 0.173
-2	0.255	0.193 - 0.277	0.203	0.145 - 0.270
-1	0.212	0.157 - 0.272	0.177	0.126 - 0.237
0	0.103	0.059 - 0.155	0.135	0.089 - 0.192
1	0.008	0.000 - 0.046	0.067	0.035 - 0.109
2	0.035	0.016 - 0.060	0.020	0.005 - 0.049
3	0.000	0.000 - 0.003	0.005	0.000 - 0.015
No. of cycles	3175		3265	
No. of pregnancies	434		435	
k	0.277		0.301	

Table 10:
Comparison of estimates of daily probability of conception

Intercourse day vs. reference day	Schwartz et al [1979]	Schwartz, MacDonald, and Heuchel [1980]	Bremme, [Bremme 1991]	Weinberg et al [1998]	Wilcox, Weinberg, and Baird [1998]	European centres
-8						0.003
-7			<0.005			0.014
-6			0.018			0.027
-5		0.04	0.076	0.100	0.04	0.068
-4	0.08	0.14	0.100	0.155	0.13	0.176
-3	0.20	0.20	0.152	0.139	0.08	0.237
-2	0.13	0.20	0.235	0.274	0.29	0.255
-1	0.21	0.34	0.270	0.312	0.27	0.212
0	0.15	0.14	0.331	0.331	0.08	0.103
1	0.11	0.07	0.065			0.008
2	0.09					0.035
No. of conception cycles	631*	103†	109	192‡	144§	434§§

* After at least 21 days of hypothermia. The "zero" point is the last day of hypothermia, following [Vincent 1964].

† Pregnancies of at least six weeks duration in a given cycle.

‡ Of which 48 (25%) early losses within six weeks and 15 clinical spontaneous abortions after six weeks from the onset of the last menses

§ The same set of data as in ‡, but excluding the 48 early losses (i.e. within 6 weeks of LMP). The probabilities used to generate the figure in [Wilcox, Weinberg, and Baird 1998] were kindly provided by Dr. David Dunson.

§§ Ongoing at 60 days from the onset of the last menses, included clinically diagnosed abortions in this period (window around BBT reference day).

Figure 1:
Daily fecundability in cycles with both BBT and mucus reference day (day 0), with 90% confidence intervals. European centres.

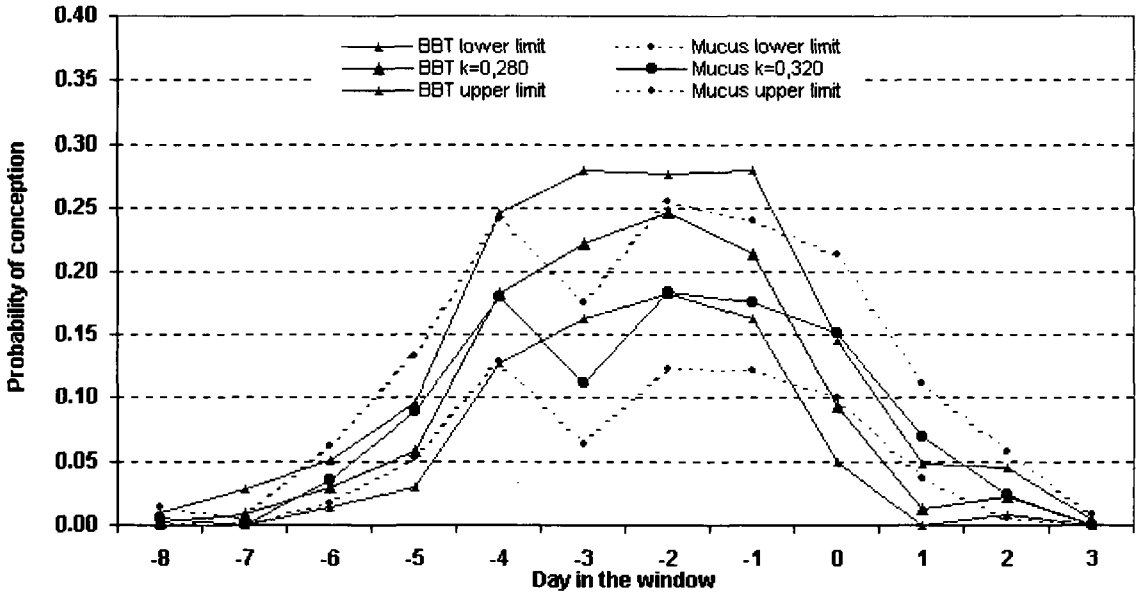


Figure 2:
Daily fecundability around the BBT reference day. Various subgroups.

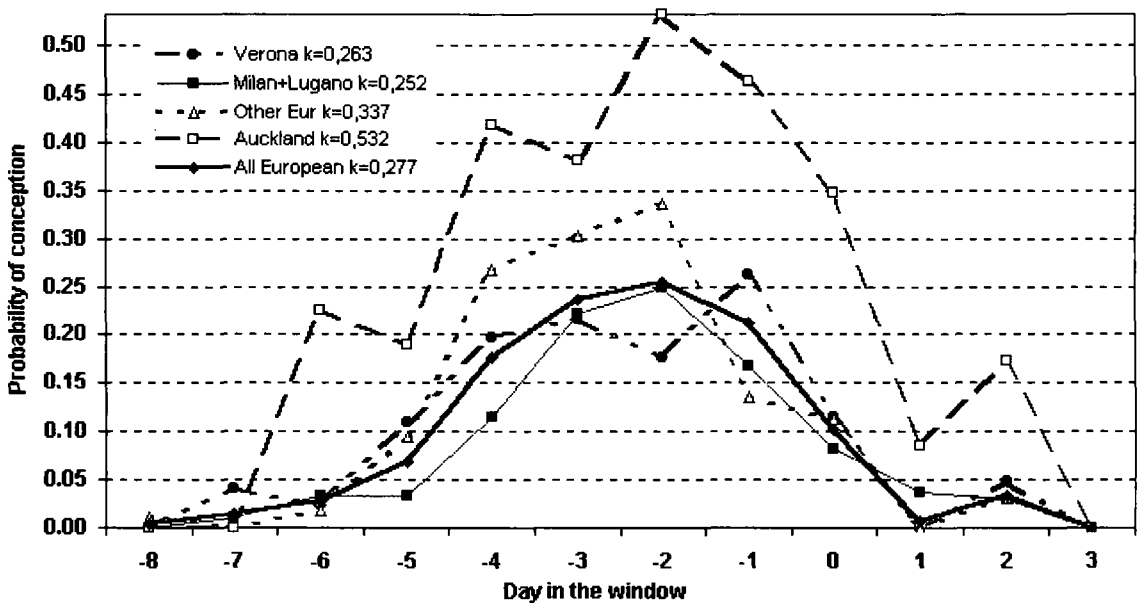


Figure 3:
Daily fecundability around the BBT reference day for women with or without previous pregnancies. European centres.

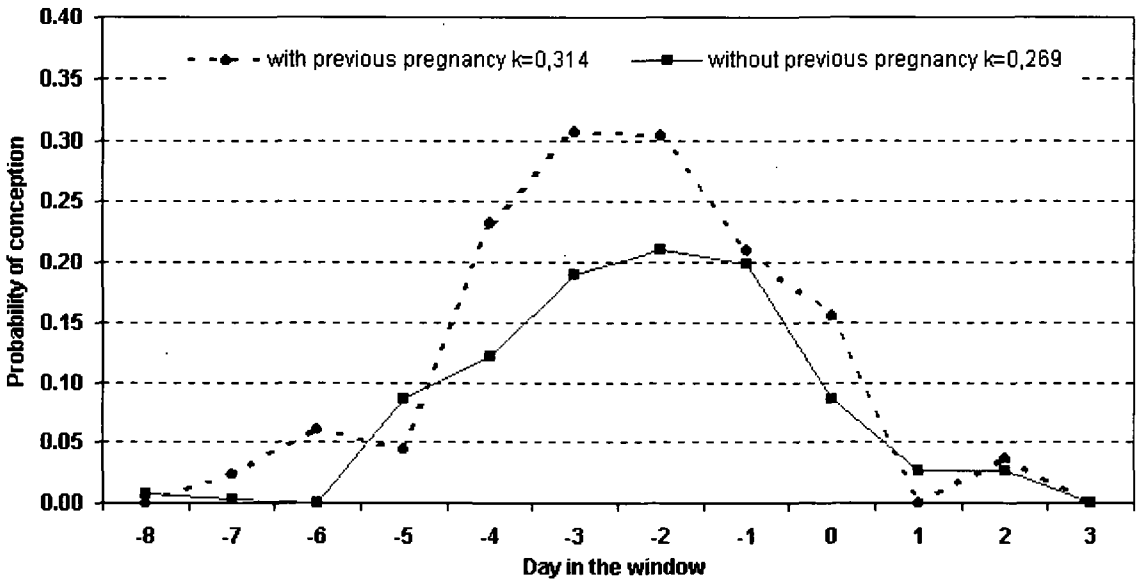


Figure 4:
Daily fecundability around BBT reference day by age classes (18-24 years, 25-34, 35-39) of women. European centres.

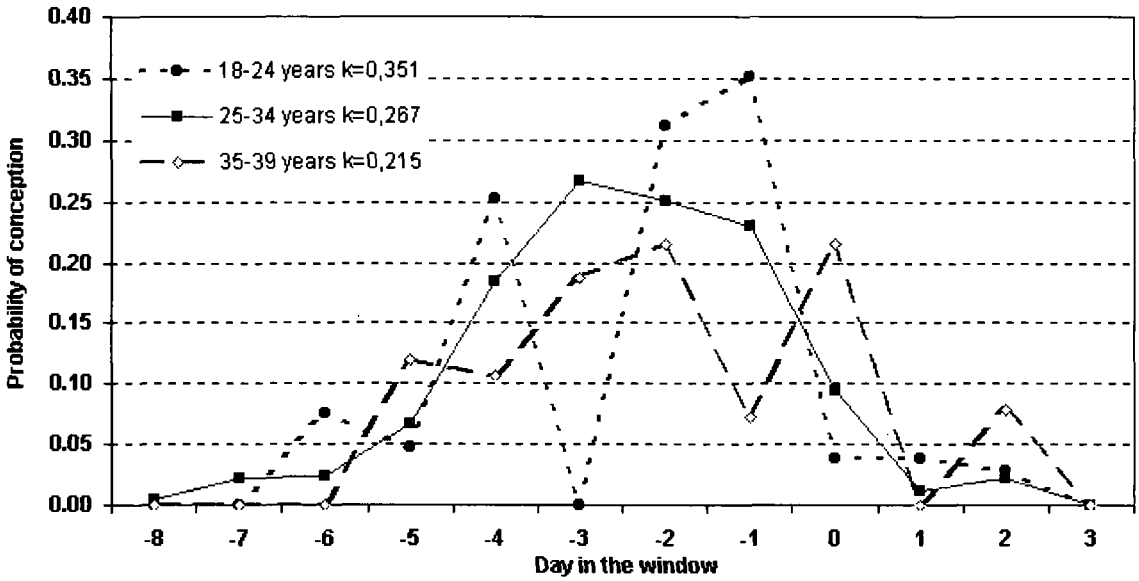


Figure 5:
Daily fecundability around BBT reference day according to the past use or no use of oral contraception. European centres.

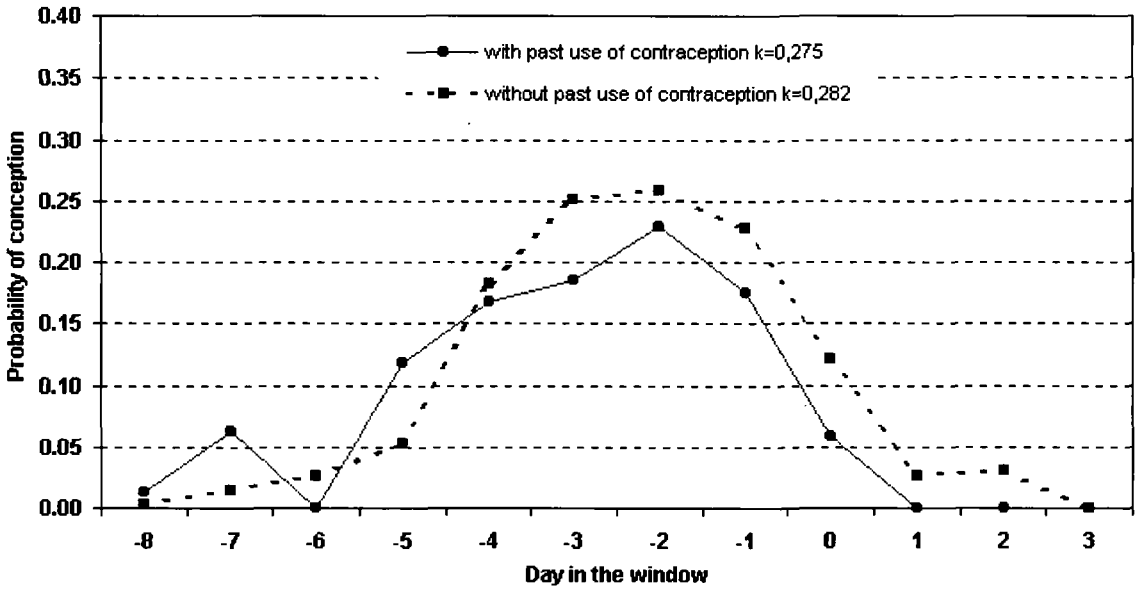


Figure 6:
Daily fecundability around BBT reference day according to the distance "BBT minus mucus reference day" (distance equal to 0 or 1 days, higher than 1 day, negative). European centres.

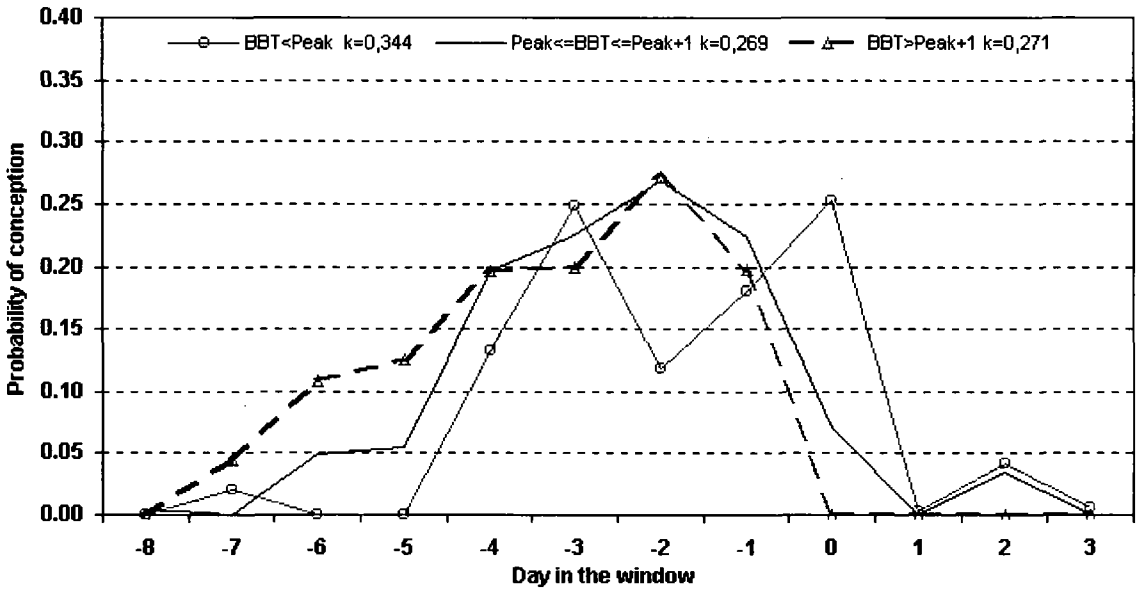
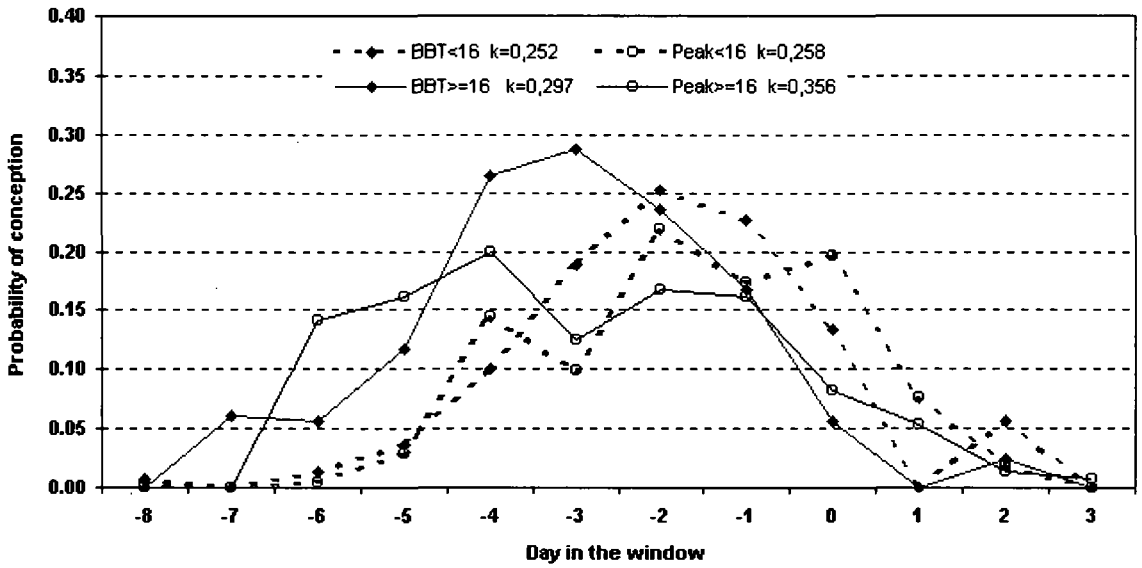


Figure 7:
Daily fecundability around BBT or mucus reference days according to the length of the respective conventional preovulatory phase (<16 days, ≥16 days). European centres.



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279: R1316–R1320, 2000.

Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring

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[1]*Department of Biological Sciences, Wellesley College, Wellesley 02481-8203;* [2]*Thermal and Mountain Medicine Division, and* [3]*Biophysics and Biomedical Modeling Division, US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760-5007*

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Coyne, Mary D., Christina M. Kesick, Tammy J. Doherty, Margaret A. Kolka, and Lou A. Stephenson. Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring. *Am J Physiol Regulatory Integrative Comp Physiol* 279: R1316–R1320, 2000.—The purpose of this study was to determine whether core temperature (T_c) telemetry could be used in ambulatory women to track changes in the circadian T_c rhythm during different phases of the menstrual cycle and, more specifically, to detect impending ovulation. T_c was measured in four women who ingested a series of disposable temperature sensors. Data were collected each minute for 2–7 days and analyzed in 36-h segments by automated cosinor analysis to determine the mesor (mean temperature), amplitude, period, acrophase (time of peak temperature), and predicted circadian minimum core temperature ($T_{c\text{-}min}$) for each cycle. The T_c mesor was higher ($P \leq 0.001$) in the luteal (L) phase (37.39 ±0.13°C) and lower in the preovulatory (P) phase (36.91 ±0.11°C) compared with the follicular (F) phase (37.08 ±0.13°C). The predicted $T_{c\text{-}min}$ was also greater in L (37.06 ± 0.14°C) than in menses (M; 36.69 ± 0.13°C), F (36.6 ± 0.16°C), and P (36.38 ± 0.08°C) ($P \leq 0.0001$). During P, the predicted $T_{c\text{-}min}$ was significantly decreased compared with M and F ($P \leq 0.0001$). The amplitude of the T_c rhythm was significantly reduced in L compared with all other phases ($P \leq 0.005$). Neither the period nor acrophase was affected by menstrual cycle phase in ambulatory subjects. The use of an ingestible temperature sensor in conjunction with fast and accurate cosinor analysis provides a noninvasive method to mark menstrual phases, including the critical preovulatory period.

ovulation; cosinor analysis; body temperature regulation; temperature telemetry

PHYSIOLOGISTS often use daily measurements of morning core temperature (T_c) as a marker to predict different phases of the menstrual cycle. Despite its variability and relative inaccuracy, this method has been used to differentiate the follicular or luteal phases of the menstrual cycle, enabling significant work on temperature regulation (2, 16), fluid volume regulation (9, 15), metabolism (14), and exercise responses (10) to be conducted. T_c monitoring has also been used in fertility assessment (3, 14) to detect impending ovulation. However, the key marker of impending ovulation, a drop in T_c, was only observed in ~50% (7) to 80% (19) of patients studied. In those studies, a single measurement of oral or rectal temperature was taken at fixed times in the morning. However, the combined influence of circadian and menstrual cycles on T_c made it difficult to identify ovulation, because a single temperature measurement was located on the sliding scale of the circadian rhythm.

The purpose of the current study was to determine whether T_c telemetry can be used in ambulatory women to identify menstrual cycle phases. We hypothesized that the sensitivity of T_c telemetry would enable detection of impending ovulation. We present a method whereby we record T_c at 1-min intervals over several days during different phases of the menstrual cycle. This methodology allows us to separate the menstrual cycle and circadian effects on T_c. We also present a methodology and procedure for quick computer analysis of the data. These methods enable us to track the changes in the circadian T_c rhythm and to identify particular phases of the menstrual cycle, such as preovulation. This technology is noninvasive, and the methods appear to be robust enough to withstand the vagaries of the normal lifestyle of ambulatory subjects. Using this methodology, we have been able to confirm both the elevation in mean T_c and the reported (5) decrease in amplitude of the circadian T_c rhythm in the luteal compared with the follicular phase. In addition, we have documented an overall decrease in T_c and the predicted minimum T_c ($T_{c\text{-}min}$) just before the urinary LH peak.

METHODS

Eumenorrheic female subjects between the ages of 22 and 43 yr were recruited from a population of college students and staff from Wellesley College and the US Army Research Institute of Environmental Medicine, without bias for race or ethnicity. The study was approved by the Institutional Review Boards of both institutions, because recruitment and

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Table 1. *Data collection times*

Phase of Cycle	Recording Days Based on a 28-Day Cycle
Menses	4 consecutive days—*days 27, 28,* and *1, 2*
Follicular phase	3 consecutive days within *days 4–9*
Periovulatory phase	4 consecutive days within *days 10–18*
Luteal phase	3 consecutive days within *days 19–24*

work occurred at the two locations. Subjects were nonsmokers; were not taking oral contraception or chronic non-steroidal anti-inflammatory drugs such as aspirin or ibuprofen, or melatonin or herbal supplements; and maintained a regular sleep-wake cycle. The presence of ovulatory cycles was documented by obtaining oral baseline temperatures with a digital thermometer at normal arousal time (usually between 0600 and 0730) for a complete cycle before testing and also during testing. T_c was monitored in each subject under her normal living conditions at four phases of the menstrual cycle (Table 1) by use of a calibrated temperature telemetry pill (Human Technologies, St. Petersburg, FL). The silicone-coated pill was easily swallowed with water and passed through the gastrointestinal tract in an average time of 3 days. A small amount of carbohydrate was eaten to move the pill into the intestines. The pill transmitted the local internal temperature to a receiver/datalogger (FitSense Technologies, Wellesley, MA), which was worn in a padded waist pack. Data continued to be collected while the subjects showered and dressed, if the receiver was placed within 4 feet of the subject. From our knowledge of the oral temperatures in the previous cycle and from continued monitoring of oral temperature, we attempted to begin data collection on the days noted in Table 1. Each subject received 3–4 precalibrated pills per session. She monitored the receiver for a loss of signal and then ingested another pill while in contact with one of the research team. Collection continued for 3–4 days or until the last pill was lost (≤7 days). The receivers stored ≤8 days of data, which were collected each minute. Data were downloaded into an IBM-compatible computer at the end of each session and transferred into Excel files. Subjects tested their urine for luteinizing hormone (LH) each morning and evening with a commercially available test stick (courtesy of Carter-Wallace, Cranbury, NJ) to assess the periovulatory period. Such tests are a semiquantitative indicator of rising and falling urinary LH levels during ovulation.

The T_c data were subjected to cosinor analysis with custom software (8) developed in the MatLab (Mathworks, Natick, MA) programming environment by use of an IBM-compatible computer (>300 MHz). The program works on Excel data files and automatically removes extraneous data (temperatures <35°C and >40°C), codes the sleep periods, calculates the days relative to the LH peak, and compiles the results in Excel worksheets. Filtering the data (1, 2, or 4 h) with fast-Fourier transform had no effect on circadian parameters. Several 24- and 36-h data segments (noon to noon, midnight to midnight, noon ± 18 h, and midnight ± 18 h) were tested. We selected the 36-h segments of the data between noon and ±18 h, because these had the best fit as judged by correlation (r^2) values. The program returns 24-h cosine segments for plotting midnight to midnight, as well as the mesor, amplitude, period, and acrophase for each segment. The program also provides the maximum ($T_{c\text{-peak}}$) and the $T_{c\text{-min}}$ for the cosine curve fit. All parameters were tested for significant differences using a one-way ANOVA for a repeated-measures experimental design. A Student-Newman-Keuls post hoc test was done to determine critical differences between phases.

RESULTS

Data were collected from four subjects over 11 menstrual cycles (Table 2). In several cases we missed the periovulatory changes on the first attempt and had to collect during a subsequent cycle. The circadian rhythms in T_c for each subject are graphed in Fig. 1, *A-D*. The mean T_c for each graph is indicated by the dotted line; however, this value could be biased by the number of observations in each phase of the cycle. Solid horizontal lines at the top of each graph represent the sleep periods. The women in this study maintained a relatively consistent sleep/wake schedule, when one considers the vagaries of normal family life. The shifts in mean T_c and change in amplitude of the circadian rhythm throughout the cycle can be clearly recognized in each of the graphs. On visual inspection, several consistent patterns are evident in the graphs. First, the daily mean temperature (mesor) was higher during the luteal phase than during the follicular phase. Second, the daily amplitudes were damped in the luteal compared with the follicular phase. Third, before the LH peak, the daily $T_{c\text{-min}}$ reached its lowest value (nadir). Although T_c maximum values were also suppressed during this phase, these differences were more obvious when we looked at the nadir for each day rather than the peak. Statistically, the mesor ($P < 0.001$) and $T_{c\text{-min}}$ ($P < 0.0001$) were significantly higher, and the amplitude was significantly lower ($P < 0.005$) in the luteal phase of the cycle compared with the three other phases (Table 3). The preovulatory phase was notable in that both the mesor ($P < 0.001$) and the $T_{c\text{-min}}$ ($P < 0.0001$) were the lowest temperatures seen throughout the cycle (Table 3). There were no differences in the period of the circadian T_c rhythm among the four phases of the cycle. The r^2 values in Table 3 are averaged over all of the daily r^2 values for 36 h and over all subjects for the given phase. The overall mean (±SD) for the r^2 values was 0.83 ± 0.1, $n = 72$.

DISCUSSION

We have described and tested a methodology for recording the circadian core temperature rhythm in ambulatory subjects for extended periods of time. This has been coupled with a fast, reliable method for applying cosinor analysis to the resulting data files. Using these methodologies, we have confirmed the effects of the female reproductive hormones on the mesor and amplitude of the circadian T_c rhythm during the follicular and luteal phases. More importantly, this method

Table 2. *Subject data*

Subject	*S01*	*S03*	*S05*	*S07*
Age, yr	35	43	22	36
Ht, m	1.61	1.65	1.64	1.52
Wt, kg	75.9	72.5	88.4	56.8
Cycle length, days	29, 29	26, 26	30, 31	29, 30
LH peak, days	15, 15	17, 21	18, 18	14, 17

LH, luteinizing hormone.

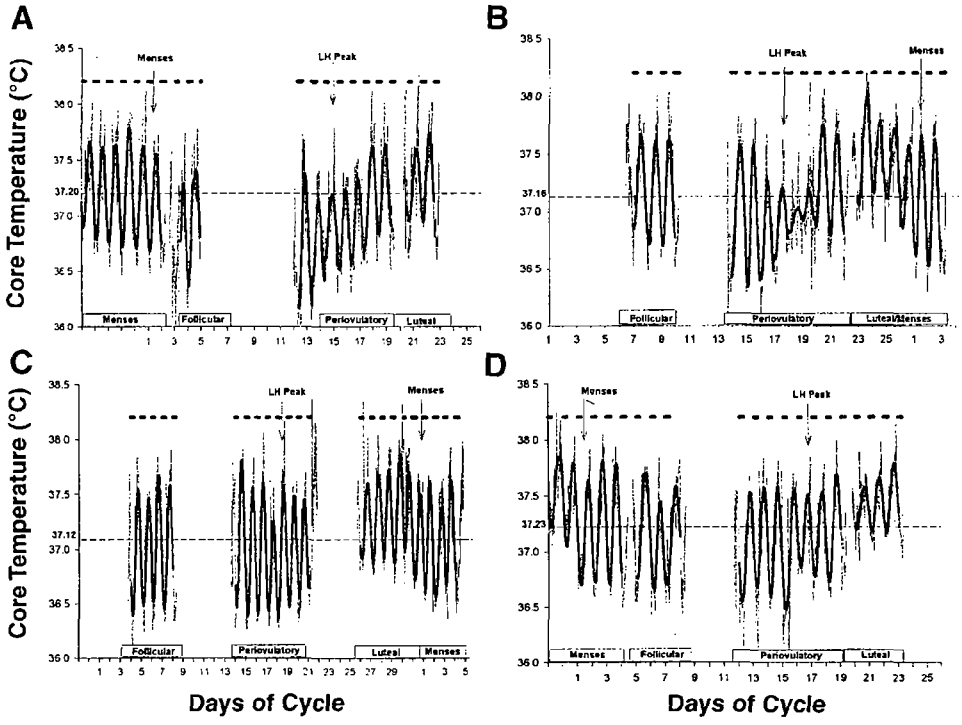

Fig. 1. Core temperatures collected every minute during selected phases of the menstrual cycle. The fine gray line is a plot of the individual data points; the darker line is a sequence of 24-h segments of individual 36-h cosinor fits. The light dashed horizontal line is mean temperature for the combined data in each graph. The dashed heavy line (*top*) indicates periods of sleep. Arrows indicate either the beginning of menses or day of the urinary luteinizing hormone (LH) peak and are so marked. Phases of the menstrual cycle are indicated below graphs. *A*: *subject S01*. Data are from cycles L (luteal/menses and follicular), J (periovulatory), and A (luteal). *B*: *subject S03*. Data are from phases A (follicular, luteal/menses) and D (periovulatory). *C*: *subject S05*. Data are from phases B (follicular, luteal/menses) and A (periovulatory). *D*: *subject S07*. Data are from phases A (menses, follicular, luteal) and C (periovulatory).

clearly demonstrates the fall in both the mesor and $T_{c\text{-}min}$ 1–2 days before the surge of urinary LH.

Clinically, in fertility studies, a rise in oral morning temperature has been used to confirm ovulation and can also be used to grossly predict a time frame for conception. The present data confirm the rise in mesor and the reported decrease in amplitude of the circadian temperature rhythm in the luteal phase of the cycle, which were based on single 24-h segments of measurement (5, 11, 13). However, the current data indicate that both the rise in mesor and decrease in amplitude are not immediate responses but adjust over a 4- to 6-day time frame, which makes it difficult to pinpoint ovulation.

On the basis of observation of oral temperature, prior evidence suggested that ovulation might be preceded by a drop in T_c (7, 14, 19). More recently a decreased regulated body temperature has been associated with the time of the preovulatory estrogen rise (17) and with estrogen replacement in postmenopausal women (4, 18). The data reported here unequivocally demonstrate a significant decrease in both the mesor and the $T_{c\text{-}min}$ within 1 and sometimes 2 days before the urinary LH surge. This temperature drop occurs about 24–48 h before ovulation, and if measured accurately, could provide an important noninvasive tool for predicting ovulation for fertilization studies.

Although we did not measure the plasma levels of estrogen directly, we predict that the fall in $T_{c\text{-}min}$ just before the urinary LH surge is due to the preovulatory estrogen surge. A good correlation has already been established between increased estrogen levels and lowered core temperature in postmenopausal women (4, 12, 18), and the addition of progesterone to these subjects reversed the hypothermic estrogen effect (12).

Although the transition in circadian T_c rhythm from the follicular to luteal phase may take up to 6 days, the transition from luteal phase to menses is relatively rapid and consistent across subjects. For example, the mesor decreased significantly within 24 h and continued to fall during the next 24 h. In three of the four subjects, the amplitude had increased within 24–48 h

Table 3. *Summary values for the four phases of the menstrual cycle*

Phase	Mesor	$T_{c\text{-}min}$	Amplitude	Period	Acrophase	r^2 Fit
Follicular	37.08 ± 0.13	36.60 ± 0.16	0.48 ± 0.06	25.52 ± 1.49	15.56 ± 0.97	0.86
Preovulatory	36.91 ± 0.11*	36.38 ± 0.08†	0.51 ± 0.02	24.52 ± 1.08	14.92 ± 1.47	0.87
Luteal	37.39 ± 0.09*	37.06 ± 0.14‡	0.33 ± 0.07§	24.85 ± 0.74	16.24 ± 0.90	0.82
Menses	37.20 ± 0.19	36.69 ± 0.13	0.46 ± 0.05	24.35 ± 1.95	15.88 ± 1.13	0.86

Data were compiled from 4 subjects. Mean values of the 2- to 3-day collection period from each subject were averaged for each phase of the cycle: follicular, 2–3 days per subject collected from *days 4–9* of the cycle; preovulatory, 2 days per subject, i.e., the 2 days before LH peak; luteal, 2–3 days per subject collected from *days 6–8* after LH peak; menses, 2 days per subject, i.e., *days 1* and *2* of the cycle. *$P < 0.001$ vs. follicular; †$P < 0.0001$ vs. follicular, menses, and luteal; ‡$P < 0.0001$ vs. follicular, preovulatory, and menses; §$P < 0.01$ vs. follicular, preovulatory, and menses.

as well. This rapid and clear transition that takes place when both estrogen and progesterone levels are dropping is in contrast to the complex interactions and changes seen during the transition at ovulation.

In studies in which ambient light, eating schedules, and activity have been controlled, there was a demonstrable delay in the acrophase in the luteal portion of the cycle (5). Although our data suggest this trend, none of the differences in acrophase were statistically significant. This is not surprising, because changes in acrophase are masked in ambulatory subjects (1) and modified by changes in ambient lighting (6).

Ambulatory monitoring of T_c with the temperature pill can be used post hoc to identify characteristics of changing menstrual cycle phases in individual women. Although measurements of morning oral temperature have been useful for gathering general patterns, there is a great deal of variability, because the core temperature is rising rapidly from its nightly nadir. Consequently, differences in measurement time of 1–2 h can substantially alter the measured temperature and mask important changes in T_c, such as those associated with ovulation.

Regarding the analysis method, although it is based on the cosinor analysis, which has been used extensively for biological rhythm studies, we were able to test the effects of using different data segments and different levels of data filtration. From a qualitative analysis of these results, we found that the best analysis of circadian variability is to use data from 1800 of one day through 1800 on the next day to 0600 of the following morning (a total of 36 h). This provides enough data to fit both the peak and the nadir of the 24-h period adequately. We also found that filtering the data before running the cosinor analysis had little or no effect.

In summary, we propose that the use of an ingestible temperature-sensing pill in conjunction with automated cosinor analysis is an effective tool in evaluating circadian T_c rhythms in human subjects. It is particularly effective in identifying the preovulatory decline in T_c and $T_{c\text{-}min}$. In addition, we are impressed that the effects of the female reproductive hormones on the circadian pattern of T_c rhythms are so robust that the pattern can be easily quantitated in ambulatory women who are not subjected to controlled lighting, sleep/wake patterns, or activity.

Perspectives

During the last 10 years there have been an increased number of investigations into women's physiology, psychology, and social interactions, but many of these studies are confounded by a lack of the hormonal status of the subjects. Although measuring blood levels of hormones is an ideal solution, it is often difficult to collect samples or, more importantly, the procedure would seriously affect the subject's performance. The simple technique of swallowing a telemetric pill and analyzing the changes in the subjects' circadian core temperature rhythm provides a relatively simple, yet accurate, means of assessing cycle phases, i.e., follicular vs. luteal. In addition, it opens up a means of documenting the preovulatory rise in estrogen as evidenced by a decline in core body temperature, and in turn providing an opportunity to investigate phenomena that might be occurring during this critical time in the cycle.

We thank the volunteers for participating in this study, Anjali Rao for data analysis, Robert Wallace for statistical advice, and Carter-Wallace, for supplying the LH test sticks.

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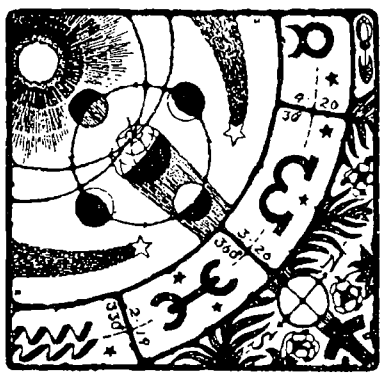
The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Human subjects who participated in these studies have given their free and informed consent. Investigators adhered to Army Regulation 70–25 and US Army Medical Research and Materiel Command Regulation 70–25 on the Use of Volunteers in Research.

REFERENCES

1. **Aschoff J.** Biological rhythms. In: *Advances in Behavioral Neurobiology*. New York: Plenum, 1981, p 311–331.
2. **Barton DS.** A study of temperature and electric potentials in the menstrual cycle. *Yale J Biol Med* 12: 503–523, 1940.
3. **Barton M and Wiesner BP.** Thermogenic effect of progesterone. *Lancet* ii: 671–672, 1945.
4. **Brooks EM, Morgan AL, Pierzga JM, Wladkowski SL, O'Gorman JT, Derr JA, and Kenney WL.** Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. *J Appl Physiol* 83: 477–484, 1997.
5. **Cagnacci A, Soldani R, Laughlin GA, and Yen SSC.** Modification of circadian body temperature rhythm during the luteal menstrual phase: role of melatonin. *J Appl Physiol* 80: 25–29, 1996.
6. **Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sanchez R, Rios CD, Freitag WO, Richardson GS, and Kronauer RE.** Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. *Science* 233: 667–671, 1986.
7. **Davis ME and Fugo NW.** The cause of physiologic basal temperature changes in women. *J Clin Endocrinol* 8: 550–563, 1948.
8. **Doherty TJ, Coyne MD, Kesick CM, and Stephenson LA.** *CIRCAD: Automated Analysis of Circadian Core Temperature Data*. Natick, MA: US Army Res. Inst. Env. Med., 2000. (Tech Note No. TN-00/2)
9. **Fortney SM, Beckett WS, Carpenter AJ, Davis J, Drew H, LaFrance ND, Rock JA, Tankersley CG, and Vroman NB.** Changes in plasma volume during bed rest: effects of menstrual cycle and estrogen administration. *J Appl Physiol* 65: 525–533, 1988.
10. **Kolka MA and Stephenson LA.** Effect of luteal phase elevation in core temperature on forearm blood flow during exercise. *J Appl Physiol* 82: 1079–1083, 1997.
11. **Lee KA.** Circadian temperature rhythms in relation to menstrual cycle phase. *J Biol Rhythms* 3: 255–263, 1988.
12. **Magallon DT and Masters WH.** Basal temperature studies in the aged female: influence of estrogen, progesterone, and androgen. *J Clin Endocrinol Metab* 10: 511–518, 1950.
13. **Parry BL, LeVeau B, Mostofi B, Naham HB, Loving R, Clopton P, and Gillin JC.** Temperature circadian rhythms during the menstrual cycle and sleep deprivation in premenstrual dysphoric disorder and normal comparison subjects. *J Biol Rhythms* 12: 34–46, 1997.

14. **Rubenstein BB.** Estimation of ovarian activity by the consecutive-day study of basal body temperature and basal metabolic rate. *Endocrinology* 22: 41–44, 1938.
15. **Stachenfeld NS, DiPietro L, Kokoszka CA, Silva C, Keefe DL, and Nadel ER.** Physiological variability of fluid-regulation hormones in young women. *J Appl Physiol* 86: 1092–1096, 1999.
16. **Stephenson LA and Kolka MA.** Menstrual cycle phase and time of day alter reference signal controlling arm blood flow and sweating. *Am J Physiol Regulatory Integrative Comp Physiol* 249: R186–R191, 1985.
17. **Stephenson LA and Kolka MA.** Esophageal temperature threshold for sweating decreases before ovulation in premenopausal women. *J Appl Physiol* 86: 22–28, 1999.
18. **Tankersley CG, Nicholas WC, Deaver DR, Mikita D, and Kenney WL.** Estrogen replacement in middle-aged women: thermoregulatory responses to exercise in the heat. *J Appl Physiol* 73: 1238–1245, 1992.
19. **Zuck TT.** The relation of basal body temperature to fertility and sterility in women. *Am J Obstet Gynecol* 36: 998–1005, 1938.



THE CAUSE OF PHYSIOLOGIC BASAL TEMPERATURE CHANGES IN WOMEN

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University of Chicago and Chicago Lying-In Hospital, Chicago, Ill.

J. Clin. Endocrinol., **8:** 550–563, 1948

The authors felt that the rise in basal body temperature during the luteal phase of the normal ovarian cycle is brought about by progesterone elaborated by the corpus luteum. The artificial reproduction of the normal hormonal cycle by the substitution of estrogens and progestins resulted in a temperature curve simulating that of the natural ovarian cycle. Progesterone can be identified as the factor responsible for the rise and maintenance of the elevated temperature in the luteal phase of the cycle. A close parallel was noted between the excretion of pregnanediol, the development of the corpus luteum and the changes in basal body temperature. With the rise in temperature there is an increased output of pregnanediol. The only outstanding difference in women with artificially produced cycles was that the rise of basal temperature at the onset of progesterone therapy was more rapid and the decline more prolonged. The normal corpus luteum probably liberates progesterone more slowly and the amount of secretory activity varies with individuals.

The ovarian function following the surgical removal of the uterus was also studied by the use of basal temperature graphs. The general pattern of the curves was typical of normal ovarian activity, and progesterone activity, as measured by the urinary output of pregnanediol during a 24-hour period, was not altered. It was concluded that follicles grow to maturity, rupture, and become functional corpora lutea which have a normal life cycle even in the absence of the uterus. In the human, the uterus is not necessary for a normal hormonal cycle.

Ovulation in many, if not in most instances, occurs with the rise in temperature rather than at the lowest point prior to the rise. It is probable that follicle luteinization begins in the theca interna cells during the stage of rapid growth just prior to ovulation and becomes accelerated with the rupture of the follicle. This explanation would account for the onset of the rise in basal body temperature prior to ovulation. 8 figures.

(See comment on following abstract.—Ed.)

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Estimated maximum failure rates of cycle monitors using daily conception probabilities in the menstrual cycle

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BACKGROUND: A number of menstrual cycle monitors have been developed to detect the fertile window of the menstrual cycle, mainly for contraceptive purposes. Reliable data on most of these systems are still missing but are urgently needed because many women use them and the tested systems differ enormously in price and effectiveness. We suggest a new efficacy estimating method to evaluate cycle monitors prior to full prospective clinical trials. METHODS: Sixty-two women prospectively tested seven cycle monitors and the symptothermal method (STM) of natural family planning (NFP) but not more than two different systems at the same time. The clinical fertile window was determined by detecting the day of ovulation using daily urinary LH measurements and daily ultrasonic folliculometry. This was compared to the fertile phase predicted by the systems. Maximum failure rates were estimated for each cycle monitor and the STM, using the daily conception probability rates taken from the European Fecundability Study. Intercourse was assumed to occur on each of all falsely predicted days of infertility. RESULTS: Sixty-two women with a mean age of 31 years (range: 21–42 years) contributed a total of 122 cycles to this study. Monitors based on the microscopic evaluation of saliva or mucus had many more false infertile days than the other methods based on temperature or hormonal measurements (225 versus 42 days). The maximum unintended pregnancy rates per cycle for temperature computers were estimated to be 0.0134–0.0336, for the hormonal computer 0.1155 and for mini-microscopes 0.2313–0.2369. For the STM of NFP, there were no false infertile days. CONCLUSIONS: The STM of NFP proved to be the most effective contraceptive method to detect the fertile window among all the methods tested. The estimated efficacy of the other cycle monitors range from the temperature computers (upper level) to the hormonal computer (medium level) and the mini-microscopes with very low estimated contraceptive efficacy.

Key words: cycle monitor/hormonal computer/mini-microscopes/natural family planning/temperature computers

Introduction

There are only 6–9 days of the menstrual cycle on which intercourse may result in pregnancy. Various devices or cycle monitors have been developed to detect the fertile window in the menstrual cycle (Freundl *et al.*, 1992; Barbato *et al.*, 1993) in order to time intercourse to avoid or to achieve a pregnancy. Recent prospective studies have estimated daily conception probabilities in the cycle (Bremme, 1991; Wilcox *et al.*, 1998; Colombo and Masarotto, 2000; Wilcox and Dunson, 2000; Wilcox *et al.*, 2001). The idea is to estimate failure rates of such cycle monitors used to avoid pregnancy by relating the predicted fertile days to the clinical fertile window detected by ultrasound and urinary LH and daily conception probabilities. To our knowledge, this is the first study in which different cycle monitors have been prospectively compared to obtain reliable failure estimates for contraceptive use. An evaluation of such monitors is urgently needed since many women ask for these devices, which differ enormously in price and effectiveness.

Materials and methods

Temperature computers are devices with a temperature probe connected to a mini-computer. An internal evaluation program automatically applies rules of the temperature method of natural family planning (NFP) to predict the fertile days in the menstrual cycle. The temperature computers use a data pool of previous measurements and cycle parameters (e.g. cycle length, day of temperature shift) for calculation purposes. The hormonal computer has a photometer reading the blue signal colour generated by an antigen/antibody reaction of the test sticks for detection of the urinary

Table I. General information about the monitors to test the fertility status of a woman

Device	Method	Manufacturer	Internet address	Approximate price
PG 53	Mini-microscope, ferning pattern of saliva or cervical mucus	Aplicationes Opticas, PG/53 Paseo de Gracia. 53 E-08008 Barcelona, Spain		
PC 2000	Mini-microscope, ferning pattern of saliva	IMPCON	www.thedonna.com	60€
Maybe Baby	Mini-microscope, ferning pattern of saliva	OPTIX. Wiesenstr., 58 D-63071 Offenbach, Germany	www.maybe-baby.com	80€
Persona	Hormone computer: LH and E3G. calculation rules	Unipath GmbHAn, Lyskirchen, 14 D-50676 Köln, Germany	www.persona.org.uk	150€ (and 12€ per month for test sticks)
Symptothermal Method (STM)	Temperature, cervical mucus	Arbeitsgruppe NFP, Malteser Werke. Kalker Hauptstrasse 22–24	www.nfp.uni-duesseldorf.de	Introductory courses, 60€
Babycomp/ Ladycomp	Temperature computer, BBT and calculation rules	Valley Electronics GmbH, Wengwiese. 3 D-82438 Eschenlohe. Germany	www.babycomp-ladycomp.com	750€
Bioself 2000	Temperature computer, BBT and calculation rules	Bioself AG, Postfach CH-1226, Genf-Thonex, Switzerland	www.bioself.com	160€
Cyclotest 2 Plus	Temperature computer, BBT and calculation rules	UEBE GmbH. Zum Ottersberg. 9 D-97877 Wertheim, Germany	www.cyclotest.de	150€

E3G = estriol glucuronide: BBT = basal body temperature.

Table II. Statistical characteristics of the women per monitor or method for age (in years) and cycles (in days)

Device or method	Women	Age			Cycle length				
	n^a	$\bar{x}$	x_{min}	x_{max}	$\bar{x}$	s	x_{min}	x_{max}	x_m
PG 53	16	31.1	23	42	28.8	4.6	17	37	29.0
PC 2000	14	30.1	21	42	27.6	4.6	22	37	26.5
Maybe Baby	16	32.0	21	38	27.6	4.8	19	40	27.0
Persona	15	31.9	25	40	27.7	5.0	22	40	25.0
Babycomp/Ladycomp	16	31.0	23	42	27.6	4.3	19	37	28.5
Bioself 2000	15	30.5	21	37	30.3	5.0	24	40	30.0
Cyclotest 2 Plus	15	31.8	21	42	26.1	3.8	17	32	27.0
NFP	15	31.9	25	40	27.7	5.0	22	40	25.0

[a]A total of 62 women participated; some women tested more than one device.
$\bar{x}$ = mean: x_{min} = minimum: x_{max} = maximum: s = SD: x_m = median: NFP = natural family planning.

hormones estriol-glucuronide and LH. An internal algorithm using a database of previous cycle length and days of hormonal shifts predicts the fertile days and automatically asks for the next measurement. The mini-microscopes consist of a glass slide and a convex lens used as a microscope with an internal or external light. The user puts a small sample of saliva or cervical mucus on the slide and checks the dry sample for ferning patterns which indicates fertility. Absence of the typical patterns indicates a non-fertile day. The manufacturers of the mini-microscopes claim that 'ferning' correlates highly with rising estrogen concentrations in the serum as well as in cervical mucus and saliva and therefore predicts fertility. Table I gives an overview of the different monitors and fertility prediction methods with the principal method, details of the manufacturers' websites, costs and postal addresses.

This study was designed to test each monitor or method in 15 women who had no prior experience with the respective systems. In addition to this, the users of the symptothermal method (STM) of NFP were also beginners. They were instructed by a qualified NFP teacher. The participants were between 21 and 42 years of age with cycle lengths ranging between 17 and 40 days (Table II). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Table III. Test combinations and distribution (testing cycle)

Device/method 1	Device/method 2	Women with this combination
Babycomp/Ladycomp	Maybe Baby	5
Babycomp/Ladycomp	PC 2000	5
Babycomp/Ladycomp	PG 53	6
Bioself 2000	Maybe Baby	5
Bioself 2000	PC 2000	5
Bioself 2000	PG 53	5
Cyclotest 2 Plus	Maybe Baby	6
Cyclotest 2 Plus	PC 2000	4
Cyclotest 2 Plus	PG 53	5
NFP	Persona	15

NFP = natural family planning.

Every woman was asked to test two differently working monitors to minimize a probable bias in interpretation of partly subjective methods such as the mini-microscopes or NFP. The testing combinations are shown in Table III. Women who wished to avoid pregnancy were asked to use barrier methods additionally. The women were asked to test the system for 7–8 cycles. The first six cycles were

'learning cycles' which were necessary to set up an internal database for the temperature computers and Persona®. The seventh cycle usually was the test cycle, in which ovulation was detected by folliculometry and LH measurement in urine. However, for the mini-microscope systems for mucus and saliva observation, a training time of ≥3 months was needed and was deemed sufficient. The days predicted as fertile by each of the systems were compared with the fertile time revealed by folliculometry and detection of the LH surge in urine.

Ultrasound scanning

Using a 3.5 MHz vaginal probe, ultrasound scanning of the ovaries and follicular tracking were carried out starting from day 8 in women with generally short cycles (according to their cycle history of the last 12 months) and from day 10 in women with normal and longer cycles. Initially, the examination was performed every second day. When the follicle size reached or just passed 12 mm, the scanning was performed daily and was continued until the observation of a follicular diameter of ≥20 mm, followed by its disappearance within 24 h. Almost all ultrasound scanning (95% of cycles) was performed by the same investigator. No cycle had to be excluded because of missing values.

Hormonal assays

The LH surge in urine was determined semi-quantitatively using the commercially available monoclonal antibody test 'ClearPlan'. Urine samples were collected daily beginning at the same time as ultrasound tracking by the participants, in collecting tubes prepared with thiomersal for conservation and stored in a refrigerator until common examination of all probes in the laboratory. The day with the most intensive coloured signal was called the LH peak day.

Use of the various devices

The devices were used according to the manufacturers' instructions. Each day of the cycle was computed as fertile or infertile as predicted by the device.

Definitions

As suggested by the World Health Organization (1980), the probable fertile window is defined as day −5 to day +2 inclusively, related to the LH peak (day 0) which roughly corresponds to the day on which the dominant follicle nearly reaches its maximum diameter, and is ~1 day prior to ovulation (24–28 h). This definition of the complete and 'objective' fertile window assumes a maximum of 6 days of sperm and 24 h of oocyte survival. Time of ovulation is defined as being between maximum follicular diameter plus 12 h and LH peak + 24 h (see Table IV).

Clinical and biometric estimations, statistical analysis

If a monitor assigns a day of the cycle as 'not fertile' which is indeed fertile according to clinical examination and previous definitions, this is called a 'false infertile day'. Using the Schwartz model (which follows Barrett and Marshall, 1969), we computed 'worst case conception probabilities' for the cycles of each woman. If we suggest that on every day in the fertile window that is indicated as 'infertile' by the cycle tester, a woman has intercourse, then we get

$$P = k\,[1 - (1 - P_{-5})^{x}{}_{-5}\,(1 - P_{-4})^{x}{}_{-4} \ldots (1 - P_0)^{x}{}_0\,(1 - P_1)^{x}{}_1\,(1 - P_2)^{x}{}_2]$$

as the worst case probability. In this formula, the index i runs from −5, −4, ..., to 2, and x_i takes the value of 1 if day i is indicated as infertile by the cycle tester (assuming the woman has intercourse on such a 'false infertile' day), and x_i takes the value of 0 if this day is predicted correctly as fertile (and she had no intercourse on that day). Using the ideas outlined by Colombo and Masarotto (2000), we need the day-specific conditional conception probabilities p_{-5}, ..., p_2 (under the condition that the oocyte is fertilized) of each day of the menstrual cycle in the fertile window and we need the cycle viability k, which is roughly the maximum probability of pregnancy in any given cycle even if intercourse occurs on every fertile day in order to calculate the worst case probability, P, of becoming pregnant for every woman. For details of the model, the reader is referred to Colombo (1989) and Colombo and Masarotto (2000). They give estimates of the day-specific conception probabilities $p_i = k\,P_i$ (with p_0 denoting the conception probability of the day of ovulation).

Table IV. Estimates of day-specific probabilities of conception (with a cycle viability $k = 0.277$)

Cycle day i relative to ovulation	$pi = k\,P_i$ †	P_i	Comments
−5	0.068	0.2455	
−4	0.176	0.6354	
−3	0.237	0.8556	
−2	0.256	0.9206	
−1	0.212	0.7653	
0	0.103	0.3718	LH peak, mfd
1	0.008	0.0289	Day of ovulation
2	0.035	0.1264	

Data are from the European Fecundability Study (Colombo and Masarotto, 2000).
†From Table 10, Colombo and Masarotto (2000).
mfd = maximum follicle diameter detected by ultrasonography of the growing follicle.

Higher values of P indicate a higher risk of conception for those women who want to use such a monitor to avoid pregnancy. In this sense, the worst case probability P is also an indicator for the quality of a monitor, indicating better 'contraception quality' if P is smaller. We used this formula to obtain estimates of maximum pregnancy rates for every woman and device together with the specific values for k and p_{-5}, ..., p_2 from Table 10 of Colombo and Masarotto (2000). These values are shown in Table IV. For example, if in the test cycle, days −5, −4, −3 and 2 of the fertile window (clinically detected by ultrasound scans and urinary LH) had not been detected as 'fertile' by the device, and days −2 to 1 had been detected correctly, then

$$P = k\,[1 - (1 - P_{-5})\,(1 - P_{-4})\,(1 - P_{-3})\,(1 - P_2)] = 0.277$$
$$[1 - (1 - 0.2455)\,(1 - 0.6354)\,(1 - 0.8556)\,(1 - 0.1264)] = 0.2674$$

was calculated as the individual risk of an unintended pregnancy, which is the maximum estimated pregnancy rate in this cycle for the user of this device and is very close to the cycle viability factor $k = 0.277$. This is a 'worst case analysis' since we assume intercourse occurred in each of the false infertile days, thus maximizing the individual risk of each participant.

A quality measure (quality index, QI) can be derived using P:

$$QI = P/k$$

for each woman and device. QI ranges between 0 and 1 with small values indicating a good method for preventing a pregnancy. A value close to 1 indicates that the device or method is close to 'no method at all'. Thus, QI serves as a normalization between 0 and 1 with the cycle viability as normalizing factor. For the example above, $QI = 0.2674/0.277 = 0.9653$, indicating that the use of the device is virtually no better than 'no use of any device'.

Performing these calculations for each combination of women and devices, the means and SD of these risks and quality measures for every device were computed. For the calculation of the individual

Table V. Detection of cycle days as fertile or infertile in relation to the clinical status as revealed by ultrasound and daily urinary LH

Device/method	Women	Cycle days	Absolute numbers and rates (%)		
	n_1	n_2	False negative[a]	False positive[b]	Correct[c]
PG 53	16	460	94 (73.4)	22 (6.6)	344 (74.8)
PC 2000	14	387	65 (58.0)	31 (11.3)	291 (75.2)
Maybe Baby	16	441	66 (51.6)	71 (22.7)	304 (68.9)
Persona	15	416	25 (20.8)	68 (23.0)	323 (77.6)
Babycomp/Ladycomp	16	442	6 (4.7)	92 (29.3)	344 (77.8)
Bioself 2000	15	454	9 (7.5)	180 (53.9)	265 (58.4)
Cyclotest 2 Plus	15	392	2 (1.7)	108 (39.7)	282 (71.9)
NFP	15	416	0 (0.0)	75 (25.3)	341 (82.0)

[a]Related to total number of fertile cycle days ($n_1 \times 8$).
[b]Related to total number of infertile days ($n_2 - n_1 \times 8$).
[c]Related to all cycle days (n_2).
False negative = a clinically fertile day which was predicted as infertile by the monitor; false positive = a clinically infertile day which was predicted as fertile by the monitor: NFP = natural family planning.

risks of becoming pregnant, a *Mathematica* notebook was written for the product formula above (*Mathematica* program package from Wolfram Research for symbolic and numerical mathematics, version 4.2, www.wolfram.com). In addition, a Microsoft Excel table was written, into which the data from the notebook could be transferred to perform further statistical analysis with the SAS program package for statistics from SAS Institute (www.sas.com, version 8.2). The data from the participants were described by the usual means of descriptive statistics: we computed the means and SD of these risks and quality measurements for every cycle in which each device was tested.

For inferential statistics, the Kruskal–Wallis test as a non-parametric one-way test was used. After demonstrating significant differences for the means of the logarithms of the worst case probabilities for unwanted pregnancies between the methods, the one-factorial analysis of variance and Duncan's a-posteriori test was used to find the possible grouping of the methods according to these average conception probabilities. This was considered as the main outcome for this research. The logarithms of the probabilities were computed to homogenize the variances between the groups instead of the original values. In addition, an analysis of variance for the percentage of false negative days was performed. The results were virtually the same as the primary analysis and are not reported here.

Results

Altogether, 65 women entered the study and three women dropped out early: one woman conceived in the third cycle, one lost the device and the third withdrew for personal reasons. The mean age of the final 62 participants was 31 years (range: 21–42 years) and they contributed a total of 122 test cycles.

In all cycles, ovulation could be detected by the LH surge and maximum follicular diameter occurring on the same day (see Table IV).

In a previously published study we have compared the correlation between the symptoms of self-observation and the ovulation detected by ultrasound/maximum follicle diameter/LH (Gnoth *et al.*, 1996) in 87 cycles. The basal body temperature (BBT) rise identified according to the three-over-six rule was detected +0.92 (± 1.17) days around objective ovulation by ultrasound and LH monitoring.

Table V shows the total number of computed menstrual cycle days for each system and gives their 'false infertile' (true fertile days predicted as not fertile days) and 'false fertile' (true infertile days predicted as fertile days) days. It is obvious that the mini-microscopes had much more false infertile days than the temperature or hormonal devices.

In contraceptive use, if a system assigns a cycle as 'false infertile' and the couple have intercourse, it has a certain probability of pregnancy, depending on the cycle day relative to the ovulation. Using the formula derived from the Schwartz model, a probability of unintended conception can be calculated for each cycle, for each device or system, with the assumption that the couple have intercourse on every day with false infertile information. This value is closely related to the efficiency of the systems when used to avoid pregnancy, which is a worst case rate for unintended pregnancies since we assume that intercourse occurred on every false infertile day. Instead of an upper limit of $k = 0.277$, the quality index *QI* can be used to limit the value of t between 0 and 1. For calculation purposes, we have used the daily probability values of the European Fecundability Study reported by Colombo and Masarotto (2000).

These recently published probabilities (Table IV) correlate well with other previously published figures (Schwartz *et al.*, 1979; Bremme, 1991; Miolo *et al.*, 1993; Weinberg *et al.*, 1994). Table V summarizes the results of this worst case analysis. Values obtained from the mini-microscopes with their relatively high rates of false infertile cycle days did not differ much from the estimated cycle viability with a maximal probability for pregnancy values. These high false negative rates and low false positive rates account for their low sensitivity detecting truly fertile cycle days. In contrast, the temperature computers and the STM of NFP are highly sensitive but less specific in detecting the fertile window which accounts for their optimal use in contraception. Persona was found to have only a medium sensitivity and specificity. The non-parametric Kruskal–Wallis test showed significant differences between the different devices and fertility prediction methods ($P < 0.0001$). Using one-factorial analysis of variance together with Duncan's method of a-posteriori testing to validate a grouping for these 'worst case probabilities', the analysis showed a significant difference between three groups

Table VI. A-posteriori grouping of the risk of unwanted pregnancy (worst case per cycle pregnancy rate) and of the quality measure for the risk of unwanted pregnancy as compared to the cycle viability (maximal probability of getting pregnant) for the various systems

Device/method	Women	Grouping	Worst case rate (P)		Quality measure (QM)	
	N		x	s	x	s
PG 53	16	A	0.2369	0.0944	0.8552	0.3017
PC 2000	16	A	0.2315	0.0804	0.8356	0.2901
Maybe Baby	14	A	0.2313	0.0925	0.8349	0.3339
Persona	15	B	0.1155	0.1219	0.4169	0.4402
Babycomp/LC	16	C	0.0336	0.0692	0.1213	0.2498
Bioself 2000	15	C	0.0208	0.0714	0.0751	0.2578
Cyclotest 2 Plus	15	C	0.0134	0.0518	0.0483	0.1872
NFP	15	C	0.0000	0.0000	0.0000	0.0000

Significant differences were found between groups A, B and C ($P < 0.0001$; x = mean, s = SD).
NFP = natural family planning.

of methods: group A consisting of the mini-microscopes PG 53, PC 2000 and Maybe Baby, group B consisting of Persona only, and group C consisting of the temperature computers and natural family planning methods. We used the Kruskal–Wallis test to prove possible differences between the means of the different methods since we could not assume normal distribution of the worst case probabilities. We additionally transformed the data by adding a constant to each value and then taking the logarithm to obtaining homogeneous variances for the groups.

We performed the Kruskal–Wallis test to find possible differences in the expectations of the worst case probabilities (and thus in the quality measures) per device. We calculated the worst case probability in the test cycle of every participant. The results of the Kruskal–Wallis test for differences and the Duncan test for a-posteriori grouping were the same for the transformed as well as for the original data. In Table VI shows the descriptive statistics for the original data together with the statistical grouping for easier understanding since a table of the Kruskal–Wallis test (rankings of all women, together with the average ranking per group) does not give as much information as a table with the means and SD of the worst case probabilities and quality measures. For all women in the NFP group, the worst case probability for pregnancy was 0 (thus giving 0 also as the mean and SD of this probability in this group according to the usual formulas used for descriptive statistics). Compared with other methods, Table V shows that NFP does not predict too many infertile days to be fertile.

Discussion

We have developed a new quality index, QI, and suggest a new method to test different cycle monitors or fertility prediction methods generally used to detect the fertile window for contraception. We compared the fertile days in the menstrual cycle predicted by the different monitors to the clinical fertile window revealed by ultrasound and urinary LH measurements. Sensitivity and specificity were calculated and analysed statistically. This procedure was shown to be effective and yielded good initial estimates of maximum unintended pregnancy rates for each monitor or method. Only cycle monitors or fertility prediction methods with a low maximum pregnancy rate in this primary efficacy estimation analysis are worth undertaking in view of the effort and expense of a full prospective clinical trial. To our knowledge, to date there has been no similar approach to compare the different cycle monitors or fertility prediction methods for contraception.

Prospective efficacy studies have been carried out on a few devices. One such device, the Ovarian Monitor (Brown and Blackwell, 1980; Brown *et al.*, 1989, 1991), which we did not test here, showed a Pearl Index of 7.3 (Brown *et al.*, 1991) in a study involving 37 women with 569 cycles. With this system, the beginning of the fertile period was marked by the rise in urinary metabolites of estrogen and the end by the rise in progesterone metabolites. This system still has some technical problems and is currently not available in Europe.

The largest prospective efficacy trial of cycle monitors was done for Persona (Freundl, 1998; Bonnar *et al.*, 1999; Trussell, 1999; Trussell, 2001), involving 710 participants in three European countries. The method failure rate was estimated to be 6.4%. In the present study, the failure rate of Persona with daily intercourse on false negative days was in the middle range of all devices tested (average of 0.1155 for the worst case probability and of 0.4169 for the quality index). Essentially, a modified device is now used to identify the fertile days to achieve pregnancy (ClearPlan Fertility Monitor: Behre *et al.*, 2000; Behre, 2001; May, 2001).

Another prospective trial was reported for Bioself (Drouin *et al.*, 1994). This study included 83 women with 745 cycles. The pregnancy rate was 9.02 (Pearl Index). Another study by Flynn *et al.* (1991) involving 131 women with 1238 cycles, showed a Pearl Index of 23. However, out of 24 unplanned pregnancies, only two could be definitely considered as method failures.

For the other temperature computers tested in the present trial, only small prospective and retrospective efficacy finding studies (EFS) (Freundl *et al.*, 1992, 1998a,b) have been performed. However, it is noteworthy that the most effective devices (and the STM) in the present study are based on BBT and that the estimates from Colombo and Masarotto (2000) are likewise derived from a BBT reference point.

No efficacy studies have been performed for the mini-microscopes prior to this study.

Recent research by Braat *et al.* (1998) investigated the reliability of predicting fertile days by observing 'ferning' in

saliva. In 30 women with regular menstrual cycles, the day of ovulation was confirmed either by ultrasound or by BBT recordings. Every morning a drop of saliva was dried and assessed with a mini-microscope in group 1 (17 women) and a normal light microscope in group 2 (13 women). Tests were judged positive with the appearance of ferning or intermediate (some) ferning. The sensitivity was 53% for group 1 and 86% for group 2. They reported a strong correlation between saliva estradiol and serum estradiol values but no correlation was detected between the estradiol concentrations in saliva and the ferning pattern, and they concluded that '... the saliva ferning is unreliable for predicting the fertile period and its use should therefore be discouraged'.

The Cue Fertility Monitor uses the changes in salivary electrical resistance. Presently, it is not available in Europe but may be of interest after some technical changes. A computerized version, OvaCue, also exists. Two small studies with 42 cycles of 19 women (Moreno *et al.*, 1997) and 21 cycles of 11 women (Fehring, 1996) reported astonishing effectiveness. However, our small prospective study (Freundl *et al.*, 1996) could not prove these results.

In summary, there is an urgent need to test systems which are developed to detect the fertile window in the menstrual cycle. To undertake the efforts and expenses of a full prospective clinical trial, a primary efficacy estimation analysis as proposed in this paper should be performed. The *QI* should be ≤ 0.5 (Persona, temperature computers, STM of NFP). Systems with a *QI* >0.5 cannot be expected to have a reasonable failure rate in a prospective efficacy finding study (pEFS), should not be offered to patients and are not worth further investigations.

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References

Barbato, M., Pandolfi, A. and Guida, M. (1993) A new diagnostic aid for natural family planning. *Adv. Contracept.*, **9**, 335–340.

Barrett, J. and Marshall, J. (1969) The risk of conception on different days of the menstrual cycle. *Population Studies*, **23**, 455–461.

Behre, H. (2001) Trial protocol and sample result of a study comparing the ClearPlan Easy Fertility Monitor with serum hormone and vaginal ultrasound measurements in the determination of ovulation. *J. Int. Med. Res.*, 29 (Suppl. 1), 21A–27A.

Behre, H.M., Kuhlage, J., Gassner, C., Sonntag, B., Schem, C., Schneider, H.P. and Nieschlag, E. (2000) Prediction of ovulation by urinary hormone measurements with the home use ClearPlan Fertility Monitor: comparison with transvaginal ultrasound scans and serum hormone measurements. *Hum. Reprod.*, **15**, 2478–2482.

Bonnar, J., Flynn, A., Freundl, G., Kirkman, R., Royston, R. and Snowden, R. (1999) Personal hormone monitoring for contraception. *Br. J. Fam. Plann.*, **24**, 128–134.

Braat, D.M.D., Smeenk, J.M.J., Manger, A.P., Thomas, C.M.G. and Veersema, S. (1998) Saliva test as ovulation predictor. *Lancet*, **352**, 1283.

Bremme, J. Sexualverhalten und Konzeptionswahrscheinlichkeit (Auswertung einer prospektiven Studie zur Natürlichen Familienplanung) (1991) Thesis, Med. Fakultät der Heinrich-Heine-Universität Düsseldorf, pp. 1–52.

Brown, J.B. and Blackwell, L.F. (1980) *Ovarian Monitor Instruction Manual*. OM Research and Reference Center of Australia, Melborne.

Brown, J.B., Blackwell, L.F., Holmes, J. and Smyth, K. (1989) New assays for identifying the fertile period. *Int. J Gynecol. Obstet.*, **1** (Suppl.), 111–122.

Brown, J.B., Holmes, J. and Barker, G. (1991) Use of the Home Ovarian Monitor in pregnancy avoidance. *Am. J. Obstet. Gynecol.*, **165**, 2008–2011.

Colombo, B. (1989) Biometrical research on some parameters of the menstrual cycle. *Int. J. Gynecol. Obstet.*, **1** (Suppl.), 13–18.

Colombo, B. and Masarotto, G. (2000) Daily fecundability: first results from a new data base. *Demogr. Res.*, **315**. Internet edition.

Drouin, J., Guilbert, E.E. and Desaulniers, G. (1994) Contraceptive application of the Bioself fertility indicator. *Contraception*, **50**, 229–238.

Fehring, R.J. (1996) A comparison of the ovulation method with the CUE ovulation predictor in determining the fertile period. *J. Am. Acad. Nurse Pract.*, **8**, 461–466.

Flynn, A., Pulcrano, J., Royston, P. and Spieler, J. (1991) An evaluation of the Bioself 110 electronic fertility indicator as a contraceptive aid. *Contraception*, **44**, 125–139.

Freundl, G. (1998) Kontrazeption per Computer. Hormonmesssystem Persona– Studienergebnisse in Deutschland. (Contraception per computer. Hormone system persona–results of studies in Germany). *Fortschritte der Medizin*, **116**, 47–48.

Freundl, G., Baur, S., Bremme, M., Döring, G., Frank-Herrmann, P., Godehardt, E. and Kunert, J. (1992) Temperaturcomputer zur Bestimmung der fertilen Zeit im Zyklus der Frau: Babycomp, Bioself **110**, Cyclotest D. *Fertilität*, **8**, 66–76.

Freundl, G., Bremme, M., Frank, H.P., Baur, S., Godehardt, E. and Sottong, U. (1996) The Cue Fertility Monitor compared to ultrasound and LH peak measurements for fertile time ovulation detection. *Adv. Contracept.*, **12**, 111–121.

Freundl, G., Frank-Herrmann, P. and Bremme, M. (1998a) Results of an efficacy-finding study (EFS) with the computer-thermometer Cyclotest 2 plus containing 207 cycles. *Adv. Contracept.*, **14**, 201–207.

Freundl, G., FrankHerrmann, P., Godehardt, E., Klemm, R. and Bachhofer, M. (1998b) Retrospective clinical trial of contraceptive effectiveness of the electronic fertility indicator Ladycomp/Babycomp. *Adv. Contracept.*, **14**, 97–108.

Gnoth, C., Frank-Herrmann, P., Bremme, M., Freundl, G. and Godehardt, E. (1996) Do the symptoms of self-observation correlate with ovulation? Zentralbl. Gynäkol., **118**, 650–654.

May, K. (2001) Home monitoring with the ClearPlan Easy Fertility Monitor for fertility awareness. *J. Int. Med. Res.*, **29** (Suppl. 1), 14A–20A.

Miolo, L., Colombo, B. and Marshall, J. (1993) A database for biometric research on changes in basal body temperature in the menstrual cycle. *Statistica*, **LIII**, 563–572.

Moreno, J.E., Khan, D.F. and Goldzieher, J.W. (1997) Natural family planning: suitability of the CUE method for defining the time of ovulation. *Contraception*, **55**, 233–237.

Schwartz, D., Mayaux, M.J., Martin, B.A., Czyglik, F. and David, G. (1979) Donor insemination: conception rate according to cycle day in a series of 821 cycles with a single insemination. *Fertil. Steril.*, **31**, 226–229.

Trussell, J. (1999) Contraceptive efficacy of the personal hormone monitoring system Persona. *Br. J. Fam. Plann.*, **25**, 34–35.

Trussell, J. (2001) Measuring the contraceptive efficacy of Persona. *Contraception*, **63**, 77–79.

Weinberg, C.R., Gladen, B.C. and Wilcox, A.J. (1994) Models relating the timing of intercourse to the probability of conception and the sex of the baby. *Biometrics*, **50**, 358–367.

Wilcox, A.J. and Dunson, D. (2000) The timing of the 'fertile window' in the menstrual cycle: day specific estimates from a prospective study. *Br. Med. J.*, **321**, 1259–1262.

Wilcox, A.J., Weinberg, C.R. and Baird, D.D. (1998) Post-ovulatory ageing of the human oocyte and embryo failure. *Hum. Reprod.*, **13**, 394–397.

Wilcox, A.J., Dunson, D.B., Weinberg, C.R., Trussell, J. and Baird, D.D. (2001) Likelihood of conception with a single act of intercourse: providing benchmark rates for assessment of post-coital contraceptives. *Contraception*, **63**, 211–215.

World Health Organization (1980) WHO Task Force on methods for the determination of the fertile period: temporal relationship between ovulation and defined changes in the concentration of plasma estradiol-17β, LH, FSH and progesterone. *Am. J. Obstet. Gynecol.*, **138**, 383–390.

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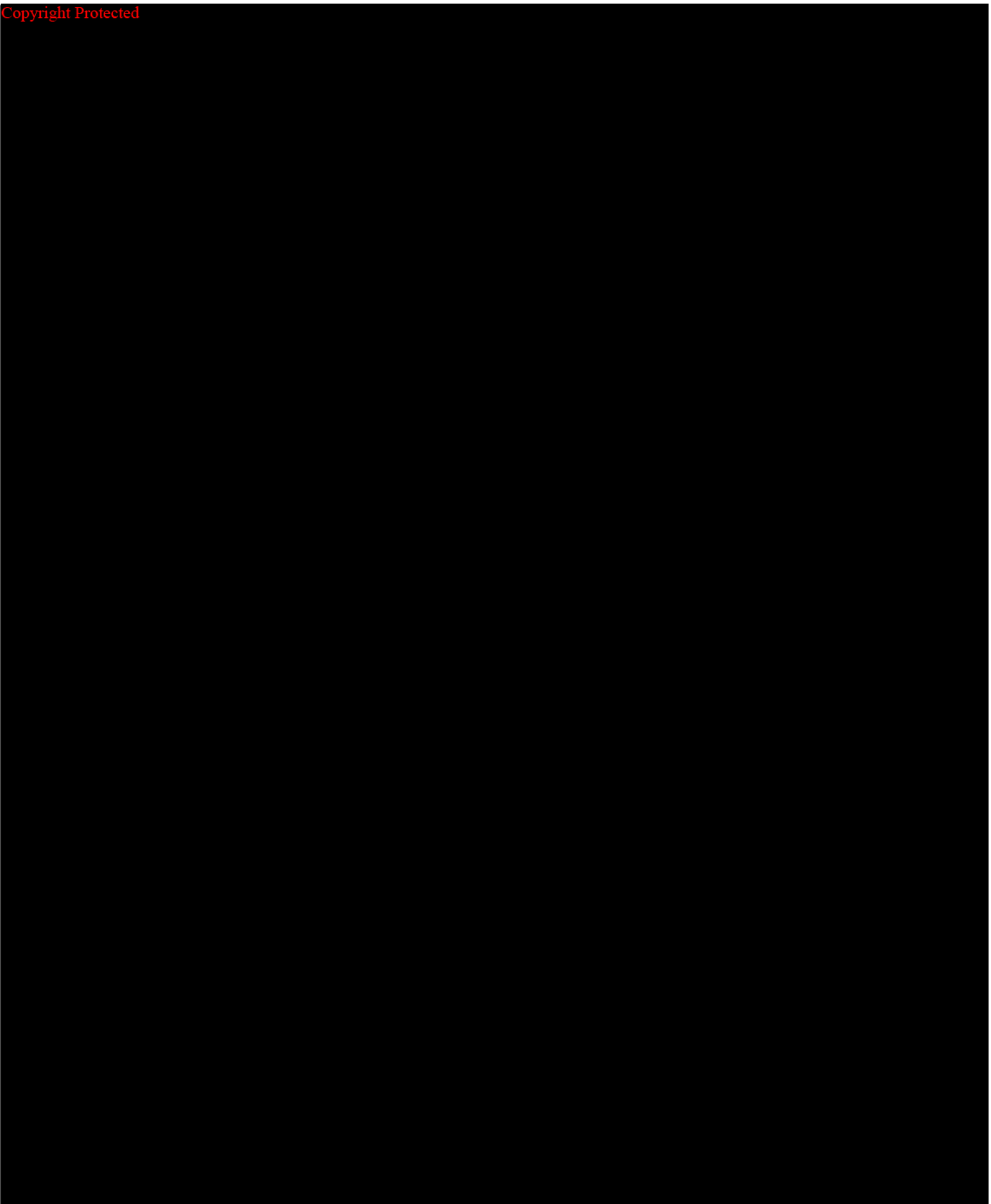
A comparison of methods to interpret the basal body temperature graph*

John J. McCarthy, Jr., M.D.†
Howard E. Rockette, Ph.D.‡

University of Pittsburgh School of Medicine and University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania

Specific criteria are given for several methods of determining the basal body temperature shift. The specific criteria selected have been coded for a uniform interpretation by computer, and interpretations have been compared for 8496 charts. Our results indicate that the method that defines the temperature shift as 0.3° F or more above the running low average for at least 3 consecutive days provides the best concurrent chart interpretation method. A method that creates a smoothed curve that transects the average of all temperatures on a completed graph provides a good retrospective method for identifying the temperature shift. Both the temperature averaging technique and curve smoothing technique identified a temperature shift in more than 95% of the charts with complete temperature readings.
Fertil Steril 39:640, 1983



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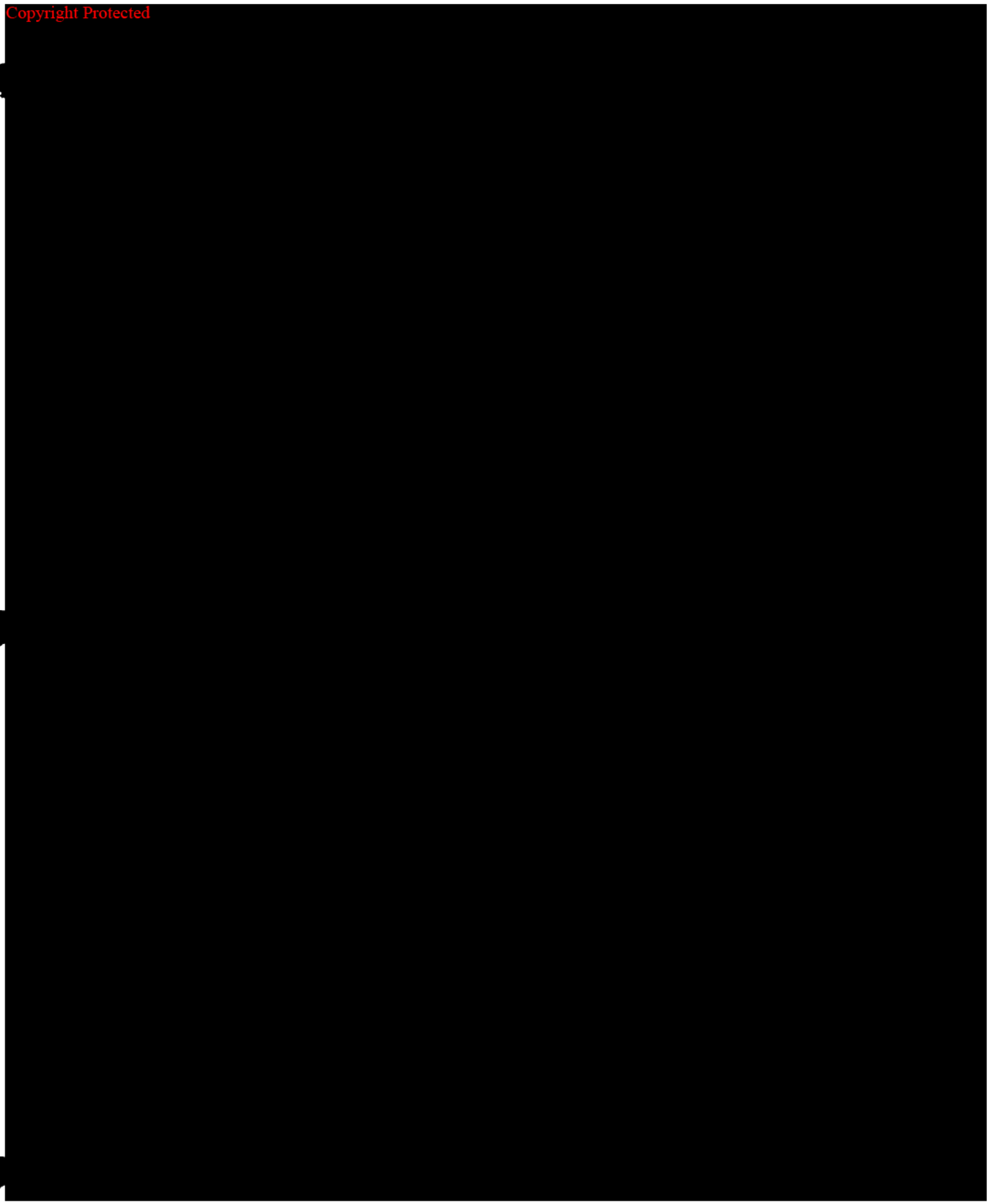

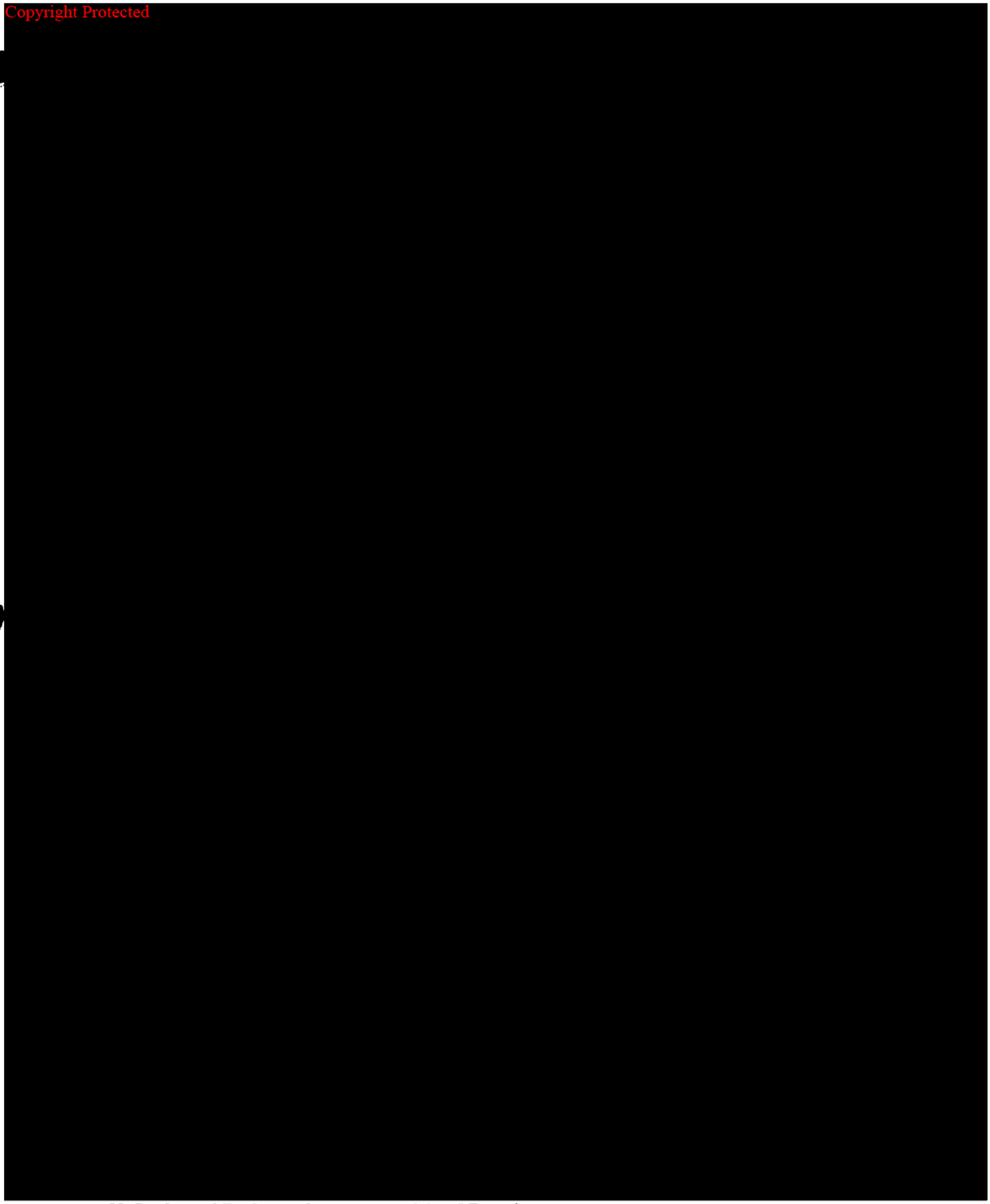

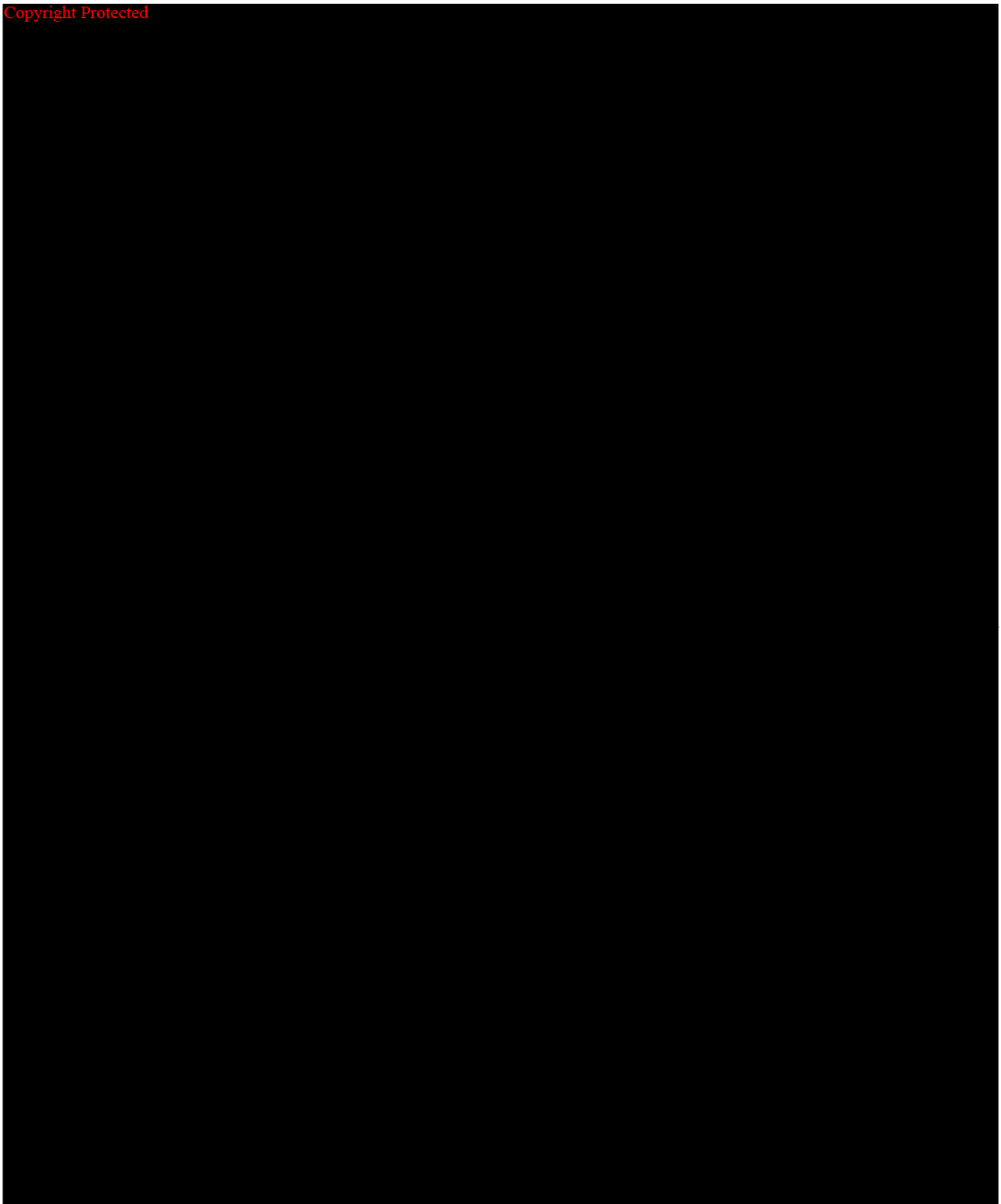

ABC of subfertility

Extent of the problem

Alison Taylor

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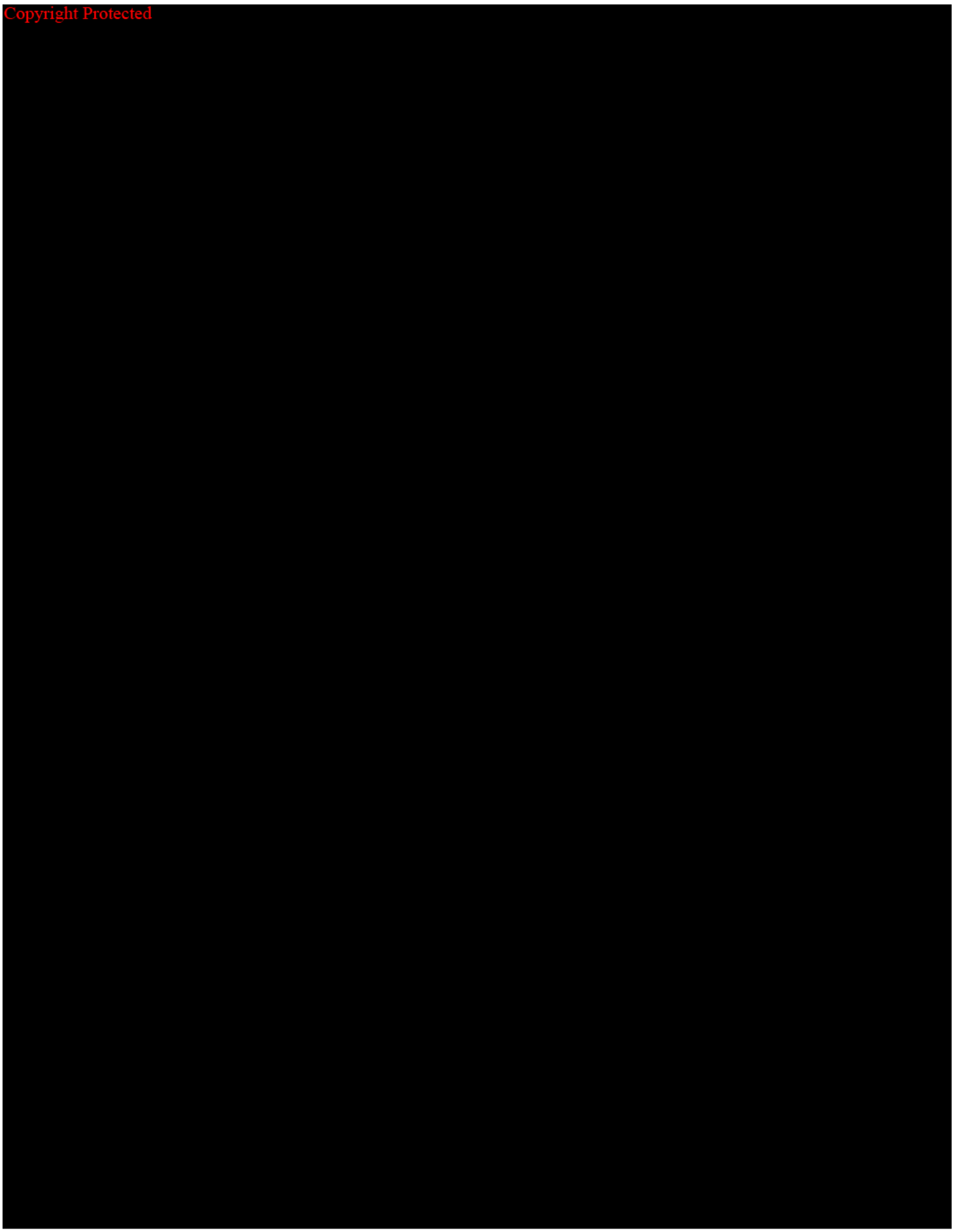

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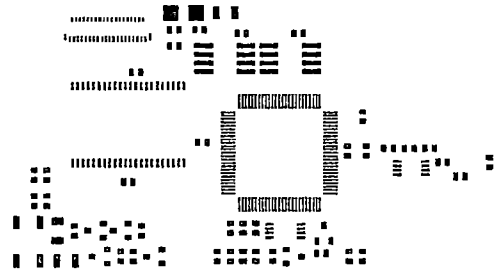
ENGINEERING DRAWINGS

(b)(4) Schematic drawing

READER

PCB LAYOUT INCLUDING SCHEMATIC



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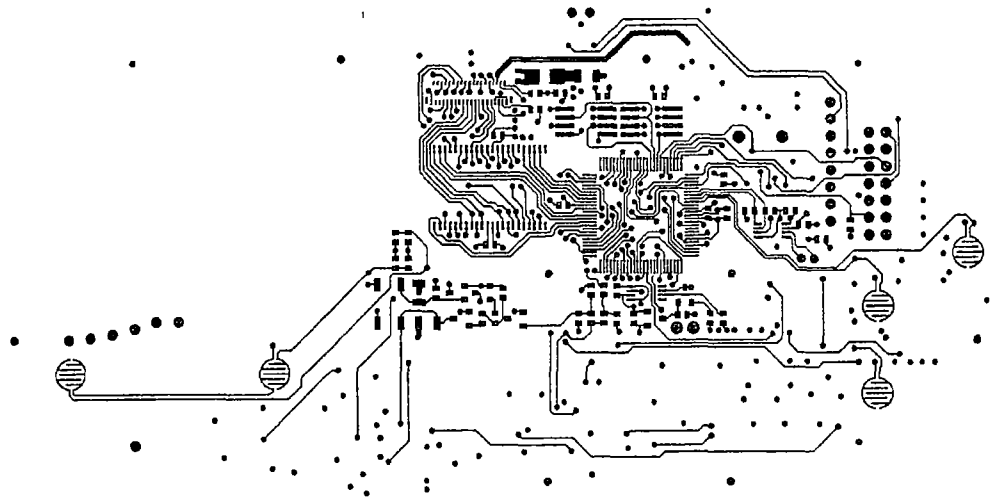
PREPARED BY CAD Data	JOB NO C12232	DATE 23-11-07	SCALE 1:1	DRG No	SHT OF

(b)(4) Schematic drawing

(b)(4) Schematic drawing



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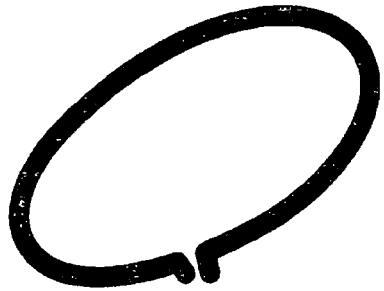

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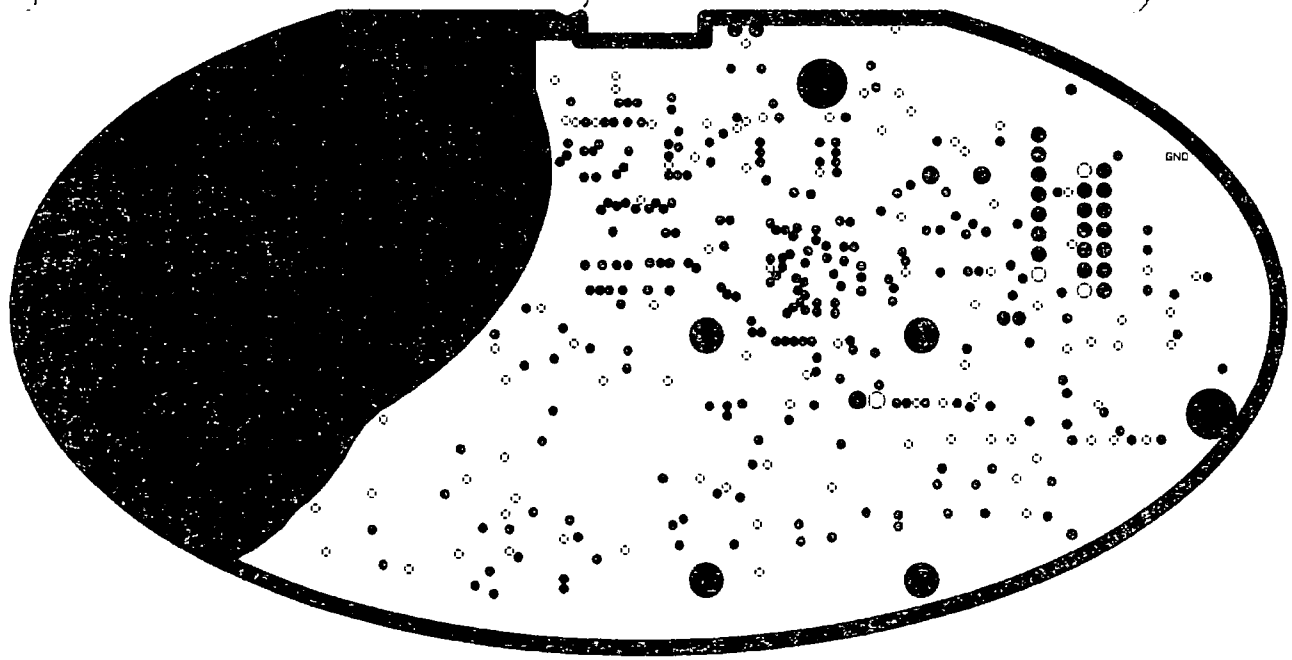

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AFMS READER PCB 2.0

C12232 23-11-07 1:1

GBE DESIGNS LIMITED					
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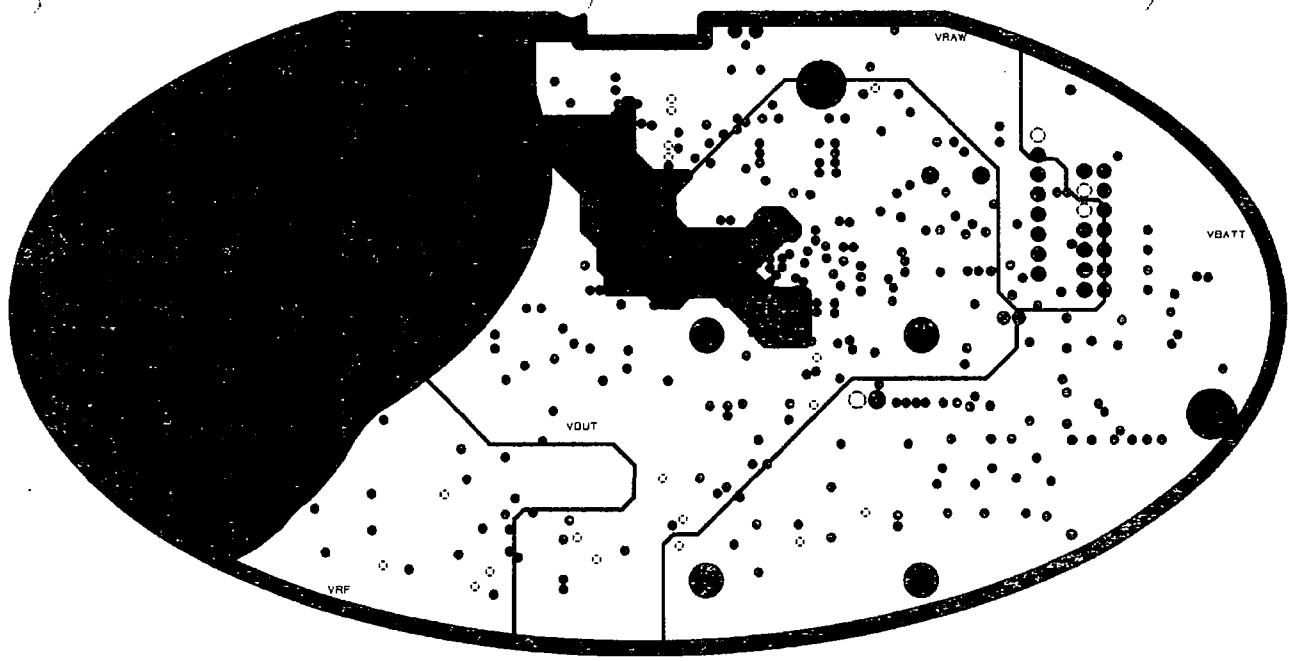

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AFMS READER PCB 2.0

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GBE DESIGNS LIMITED					
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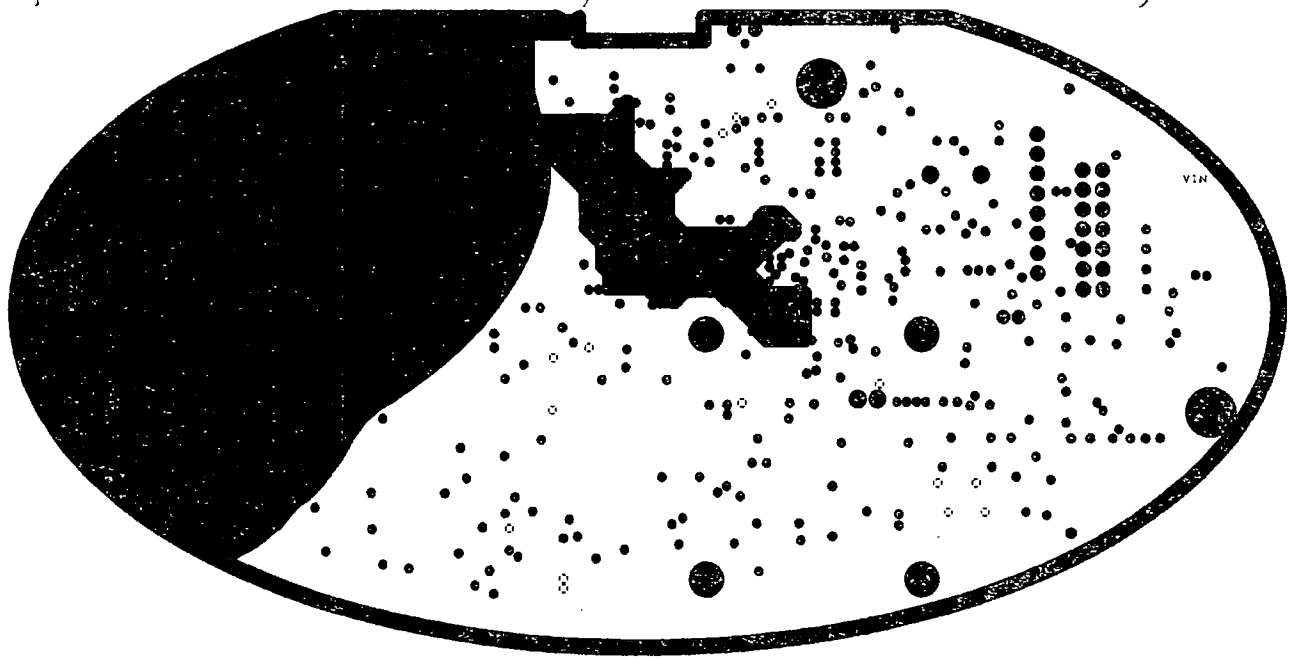

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AFMS READER PCB 2.0

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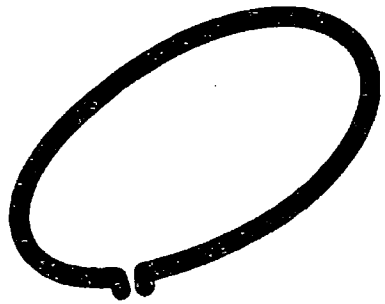

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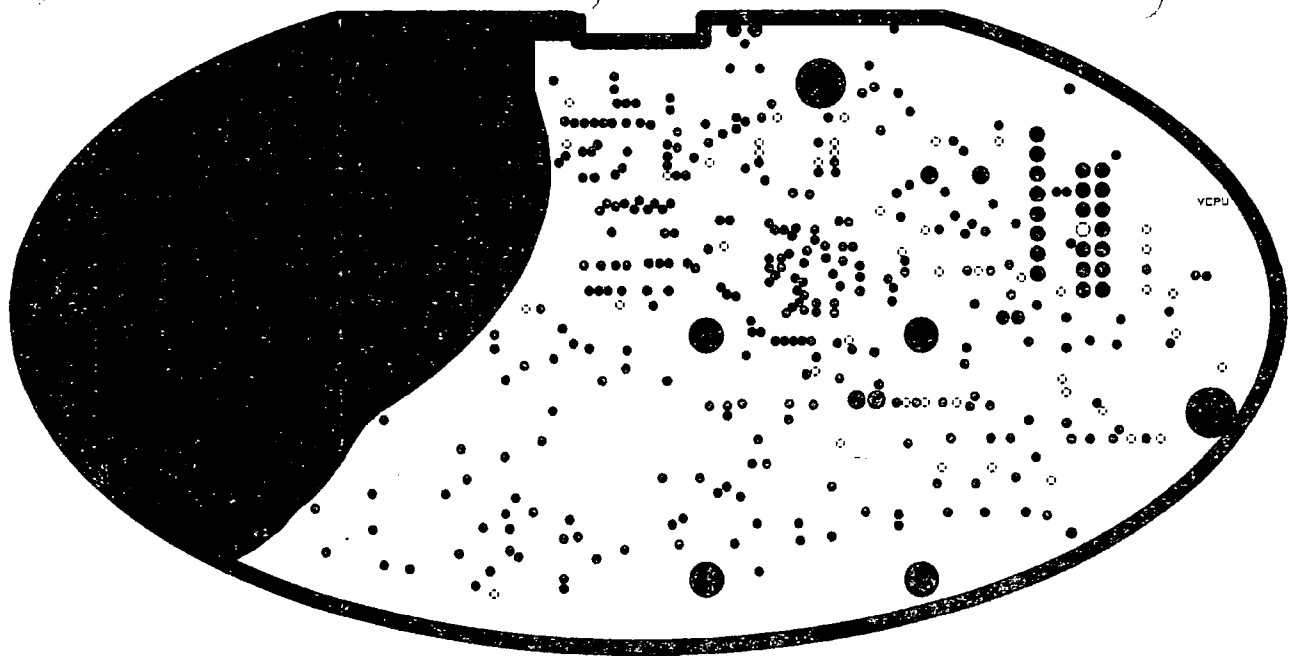

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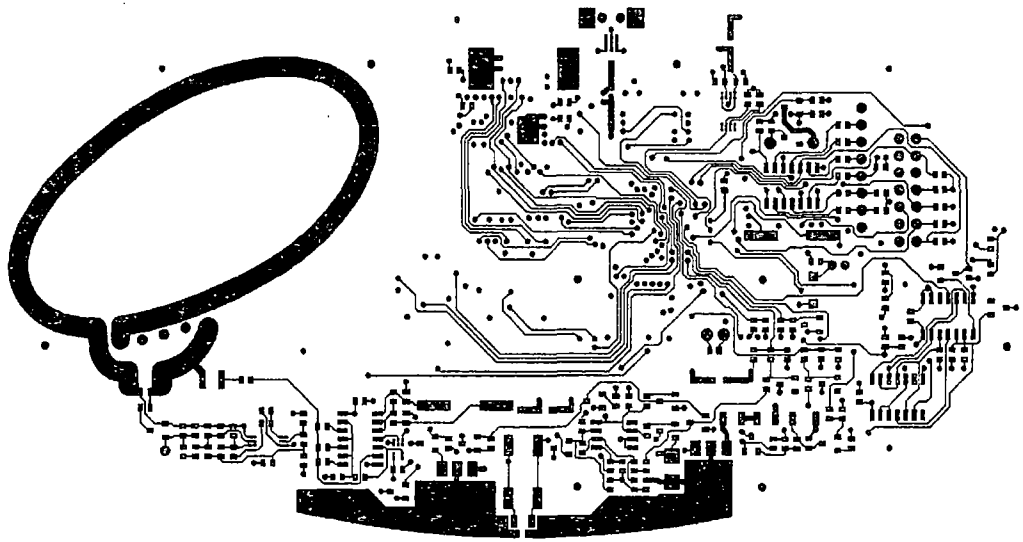

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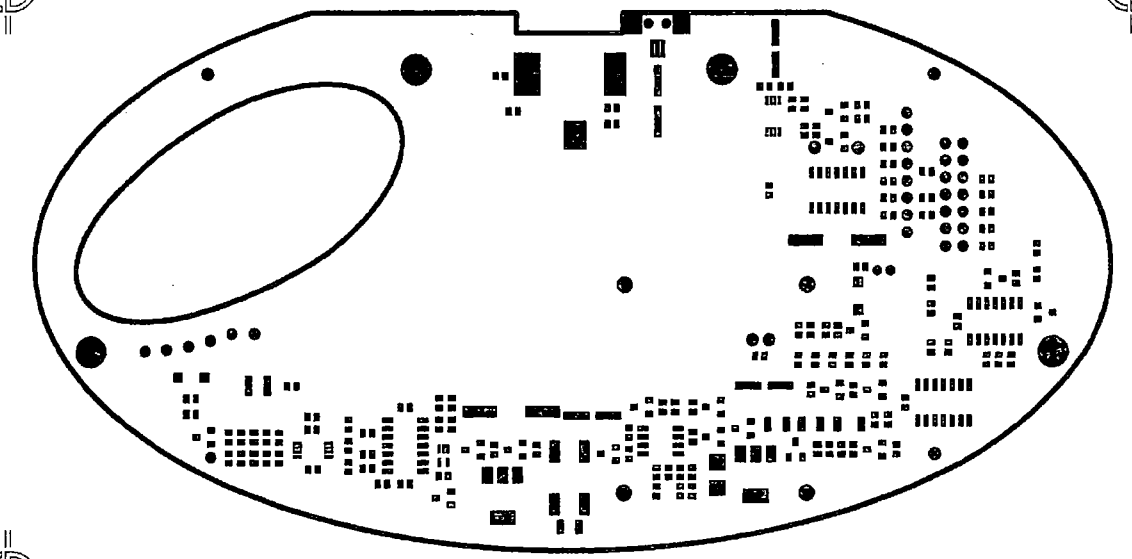

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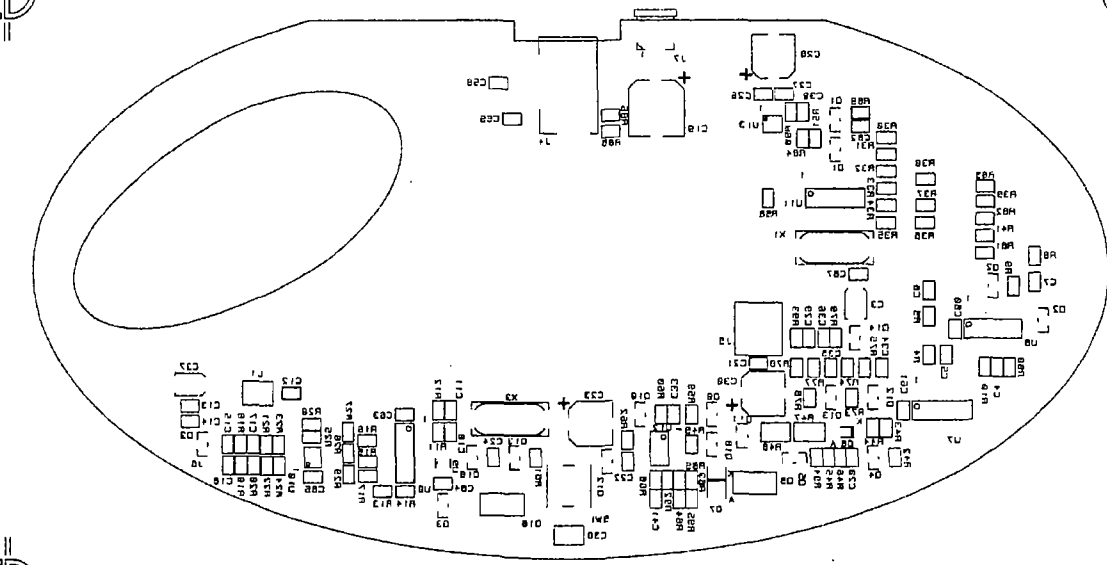

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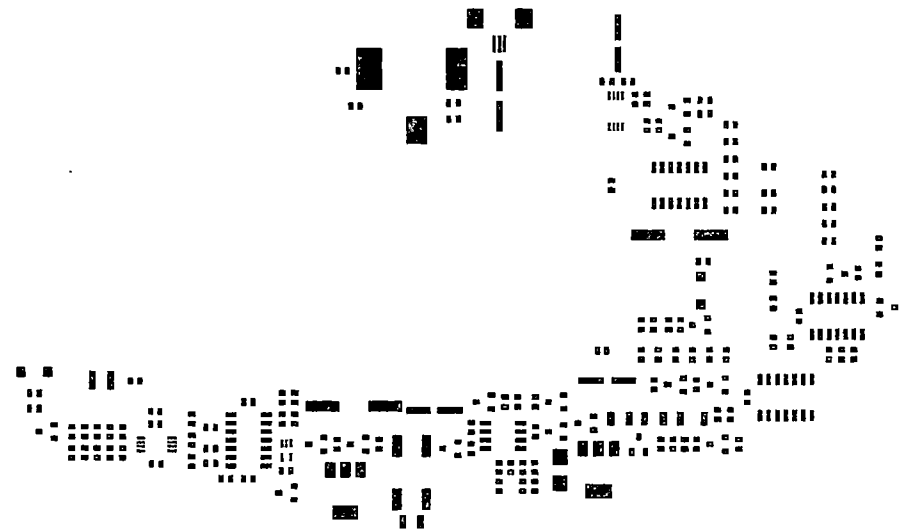

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PREPARED BY CAD Data	JOB NO C12232	DATE 23-11-07	SCALE 1:1	DRG No	SHT OF

(b)(4)

Revision 0.5 (11th September 2007)

Initial tracked version.

Revision 0.6 (18th September 2007)

Added this sheet (modification history)
C26, C36 now rated at 10V in line with C23.
Added part and package data for U10
Chip select for display from CS1 not CS0
Change footprint for U2 to match Cypress terminology
D14 is BOT23 not SOD80

Revision 0.7 (1st October 2007)

Correct serious error in pin numbering for U1
Show connection to U1.42 (HD)

Revision 1.0 (9th October 2007)

Cosmetic changes
Assign values to R29, R71, C29

Revision 1.1 (from 25th October 2007)

(Changes resulting from initial prototypes)
Apply pull-up (R68) to NMI input
Change HOLD pull-down (R48) to pull-up.
Add pull-ups to TXD, RXD and SCLK at engineering port (R81-R83)
Change reset line constant components (R4, C82)
Added second site for C286 capacitor.
Add pull-up to CPU TXD2 output (MCMTX) (R84)
Use separate resistors for LED current control
(Added R85-R88, deleted R69)
Specify part for U12 (LM393M)
C23 value reduced to 47uF
Q14 changed to a ZXM61N02 FET
Add pull-down (R89) to gate of sounder drive FET (Q1)
Swap port assignment for SPI(CS3, SPICS) and I2C(LK, IDATA
Add test point (T6) to RF demodulator
Add pull-down to backlight regulator control (R90)
Add decouplers to regulator compensation pins 1
Add series resistor for buzzer.
Add further connector for modem port.
Changes to circuit associated with U12A
Added capacitor (C41) from U12.7 to ground.
Add R92, and change divider arrangement at U12A (minute.
Changes to circuit associated with U14.7
Add bleed diode D15 resistor R92

Revision 1.2 (14th November 2007)

Changes to fast-charger current source (Q6)
Add shunt resistor across D5 (R93)
Add bleed resistor to sink (leakage current (R94)
Adjust values for R42, R45, R46
Change value of RF antenna trimmer to 33pF

Revision 1.3 (19th November 2007)

Sub-net associated with X4.1, R91.1, D1.2 is now separate.
(Previously connected to VCPU)

Doc #: 2000-CNB0003	Modification history			Approved:
Sheet: 7 of 7				
Revision: 1.3	Project: AFMS Reader. V1		Author: P Dixon. GBE Designs Ltd	
Rev. date: 19th November 2007	Assembly: Main PCB		phil@gbelectronics.com	Date:

(b)(4) Schematic drawing

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SENSOR PCB LAYOUT

INCLUDING SCHEMATIC

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MATERIALS INFORMATION

MATERIAL CERTIFICATIONS

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K122337 Vol. 2

Attachment D

CYTOTOXICITY TESTING

(b)(4)

FINAL STUDY REPORT

(b)(4) Study Protocol

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Protocol and Test Request Form

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MUCOSAL (VAGINAL) IRRITATION TESTING

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Appendix - Pathology Report

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Protocol and Test Request Form

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Protocol, Test Request Form and Amendment

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(b)(4) Study Protocol EXTRACTION TESTING

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DETERMINATION OF BIOBURDEN TESTING

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CLEANING VALIDATION TESTING

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SOFTWARE SYSTEM ACCEPTANCE TEST & TRACE SPECIFICATION

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SOFTWARE SYSTEM ACCEPTANCE TEST PROCEDURES AND RESULTS

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PREDICATE DEVICE INFORMATION

510(k) Premarket Notification

Device Classification Name	Device, Fertility Diagnostic, Proceptive
510(K) Number	K904211
Device Name	BIOSELF 2000 FERTILITY INDICATOR
Applicant	BIOSELF, INC. 7, Avenue De Thonex Case Postale 172-Ch-1226 Thonex-Geneve-Suisse,
Contact	James Pulcrano
Classification Product Code	LHD
Date Received	09/12/1990
Decision Date	10/14/1992
Decision	Substantially Equivalent (SE)
Classification Advisory Committee	Obstetrics/Gynecology
Review Advisory Committee	Obstetrics/Gynecology
Type	Traditional
Reviewed By Third Party	No
Expedited Review	

OVUSENSE CLINICAL INVESTIGATION PLAN

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K122357 Vol. 3

Attachment O

ELECTRICAL, EMC AND RADIO TESTING

(b)(4) Software requirements

(b)(4) Test Report

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REPORT ON THE EMC TESTING

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TEST REPORT ON THE SAFETY OF ELECTRICAL EQUIPMENT

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Attachment 2 Risk assessment Documents

AFMS 10-0001 Risk Management Plan 1.0
AFMS Risk Assessment Matrix V.1.4
AFMS Risk Management Report 1.1
AFMS Hazard Identification
Design Verification UOB2
Design Verification UOB4
Design Verification UOB6

Risk Management Plan

Project No: 10

Document No: 10 – 0001

Version no: 1.0

Approved By: (Title/Signature) **Date:**

Approved By: (Title/Signature) **Date:**

Contents

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OVUSENSE PERSONAL SENSOR TEMPERATURE TESTS

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RATIONALE FOR OVUSENSE DESIGN VALIDATION TRIAL DESIGN

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OVUSENSE FERTILE PERIOD DETECTION

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

OCT 1 4 1992

Mr. James Pulcrano
General Manager
Bioself Distribution S.A.
7, avenue de Thônex
Case postale 172
CH-1226 Thônex-Genève
SUISSE

Re: K904211/E
BIOSELF 2000 Electronic
Fertility Indicator
Dated: April 22, 1992 and
September 30, 1992
Received: April 28, 1992 and
October 1, 1992
Regulatory Class: Unclassified

Dear Mr. Pulcrano:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments. You may, therefore, market the device, subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (Act). General controls provisions of the Act include requirements for registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under the Radiation Control for Health and Safety Act of 1968, or other Federal Laws or Regulations.

This letter immediately will allow you to begin marketing your device as described. A FDA finding of substantial equivalence for your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market, but it does not mean that FDA approves your device. Therefore, you may not promote or in anyway represent your device or its labeling as being approved by FDA. If you desire specific advice on the labeling for your device, please contact the Division of Compliance Operations, Device Labeling Compliance Branch (HFZ-326) at (301) 427-1342. Other general information on your responsibilities under the Act, may be obtained from the Division of Small Manufacturers Assistance at their toll free number (800) 638-2041 or at (301) 443-6597.

Sincerely yours,

Lillian Yin

Lillian Yin, Ph.D.
Director, Division of Reproductive,
Abdominal, Ear, Nose and Throat,
and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

A family planning and a natural alternative available to women to accurately identify the days of fertility

The purpose of Bioself

Bioself allows a woman to approach the subject of her fertility with serenity, and enables her to confidently identify the fertile days of her menstrual cycle using a natural method.

There are just a few fertile days each month. Your own fertility is quite unique to you. It is delicate and something you should protect. It has to be your very own. Bioself offers you the opportunity to take charge of it, to manage it yourself rather than by having recourse to medical solutions or invasive options.

Freeing yourself from artificial methods is showing respect for your body. It demonstrates your ethical views and your appreciation of the serenity that comes with a harmonious sex life.

In this context, the Bioself fertility indicator is a great asset when you want to get pregnant by natural means.

It also represents a prime alternative to artificial methods of contraception such as the pill or IUD, compared to which it offers the same degree of credibility and reliability, but with the additional and ultimate advantage of having no side effects whatsoever.

Bioself – characteristics and advantages

An increasing number of women are nowadays opting for a natural method. The reasons for making this choice are wide and varied:

- Medical contra-indications (risk of phlebitis, cholesterol, triglyceride levels or high blood pressure);
- Artificial contraception methods have become uncomfortable or harmful;
- Ideological or religious conflict of conscience.

This natural option offers clear advantages from the health standpoint:

- No medical or chemical intake;
- Absence of any barrier or invasive element in the body;
- Complete absence of any side effects;
- Better understanding of the body and its fertility.

Bioself has been subjected to numerous clinical studies in Europe, Canada and in Asia. The results demonstrate 97% to 99% reliability provided the device is used according to the instructions.

BIOSELF™
PO Box • CH-1226 THONEX-GENEVE
Phone (41) 22 349 68 13 • Fax (41) 22 348 12 11
Internet: www.bioself.com • Email: admin@bioself.com

Could Bioself suit you?

Bioself is suitable for all women of childbearing age, provided that:

- The duration of their cycle is between 18 and 39 days;
- They are not using any treatment, which affects the menstrual cycle (e.g. contraceptive pill);
- They are not breastfeeding;
- No symptoms of the menopause are present;
- No medicine is being taken that could affect basal body temperature (BBT).

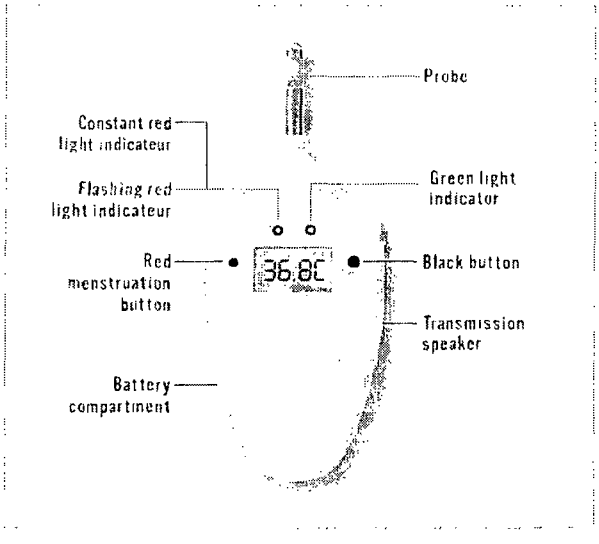
We recommend Bioself for use by adolescent girls for educational purposes so they become more aware of, and better understand, the way their menstrual cycles work. They should first acquire biphasic cycles before using Bioself for contraceptive purposes.

Bioself - the device

Bioself SA, a pioneer in fertility recognition, has been marketing this electronic device since 1986. It gives a precise indication of a woman's fertile days via the combined analysis of the length of her cycles and daily body temperature.

Only slightly larger than a mobile phone, and very easy to use, the device is made up of the following elements:

- A temperature-sensitive probe to measure your temperature;
- Two lights providing daily indications of three stages of fertility;
- A red button to record the beginning of your cycle;
- A black button giving access to various menus;
- An LCD screen for showing information.



Bioself - functionality

The temperature-sensitive probe
Its purpose is to measure basal body temperature (BBT). Temperature may be taken in the mouth, the anus or in the vagina.

The temperature thus measured can be shown on the screen at any time by simultaneously pressing the two metallic parts of the probe.

The green light shows
When the green light shows, it indicates the infertile phase of your cycle. During this phase, sexual intercourse will not result in pregnancy

The red light shows continuously
When the red light shows continuously, it is indicating the less fertile phase of your cycle. Your chances of conceiving are slight. However, if a pregnancy is not desired it is wise to use contraception.

The red light blinks
This shows that you are in the most fertile phase of your cycle. It is the ideal phase for conception.

A protective barrier is absolutely necessary for contraceptive purposes.

The black button
The black button gives you access to the additional menus available on the device. You can thus review the historical data on your temperatures, and the length of your previous cycles.

The red button for cycles
Press this button as soon as your menstrual cycle starts in order to tell Bioself that you are starting a new cycle.

The battery compartment
Bioself runs on 3 standard alkaline batteries of 1.5V (AAA/LR03), widely available in the shops.

The loudspeaker
This loudspeaker is for sending the data stored in your device to a Bioself center, where it will be printed out in graphs and sent to you (by post, fax, e-mail).

Bioself - what is it for?

The Bioself stores and analyzes the many signs of changes happening to your organism during your menstrual cycle. It calculates and identifies your fertile days without resorting to invasive means, and lets you listen to your body.

Do you want to get pregnant?
The red light shows continuously
It means you are in the less fertile phase of your cycle, and the probabilities of conception are slight.
The red light blinks
This shows that you are in the most fertile phase of your cycle. It is the ideal phase for conception. Bioself has precisely identified the various phases of your ovulation, and calculated in advance the days of optimal fertility. You can therefore plan the frequency with which you have intercourse. It is recommended to make the intervals between having intercourse short.

BIOSELF™
PO Box • CH-1226 THONEX-GENEVE
Phone (41) 22 349 68 13 • Fax (41) 22 348 12 11
Internet: www.bioself.com • Email: admin@bioself.com

Are you looking for contraception?
The green light shows
It means you are in the infertile phase of your cycle. During this phase, sexual intercourse will not result in pregnancy.
The red light shows continuously
It means you are in the less fertile phase of your cycle. Your chances of conceiving are slight. However, if a pregnancy is not desired it is wise to use contraception.
The red light is blinking
This shows that you are in the most fertile phase of your cycle. A protective barrier is absolutely necessary.

Bioself - how should I use it?

Using Bioself is as simple and reliable as taking a pill every day.

At the beginning of each menstrual cycle
As soon as the cycle starts, you press the red button for *menstruation to record the start of your new cycle.*

When you wake up in the morning
When you wake up, and before getting up or doing anything, you take your basal temperature. You can do this in the mouth, the anus or the vagina.

When taking your temperature in the mouth, put the probe under the tongue and in the middle of your mouth, which needs to be shut. It just takes two minutes for Bioself to take the measures of body temperature it needs to accurately determine your BBT. A beep indicates the end of the process, and that the measure has been correctly verified and recorded.

The time when you took your temperature decides the time frame available for taking your temperature the following morning. Bioself allows for an interval of 4 hours: 2 hours before and 2 hours after the time when you took your temperature on the previous day.

For example: On Monday, you took your temperature at 7:00am
On Tuesday, you can take it between 5:00am and 9:00am
The discreet Bioself warning will go off at 7:00am.

For best results, we recommend taking your temperature at about the same time every day.

The good news
When the green light for infertile days is on, you may not have to take your temperature every day. There are between 12 and 18 of these days in a healthy woman's cycle.

Different time zones
In the event of changing time zones, working irregular hours, etc., the time frame for taking your temperature can be adjusted to your needs. Take a look at the instructions under the "Hour" menu.

Bioself - temperature curves

The temperature data for the previous 12 menstrual cycles that are stored in your device can be printed out in the form of curves on a graph. You just need to call a Bioself center for this service.

This information is of great value to your doctor in cases of infertility or for determining the likely term of the pregnancy.

The temperature curve can also be useful as an indication of pregnancy. In this case, Bioself shows a specific message (BABY?), and when the curve is printed out the theoretical date of the term will be calculated.

To communicate the data stored in your device to a Bioself center, you need to do the following:

- Call the Bioself center;
- Select the *TEL* menu on your device and follow the instructions;
- When Bioself sends the transmission tone, put the Bioself loudspeaker (on the back of the device) on the telephone handset;
- Wait for the transmission to be completed: this happens when the tone signal stops.

The data stored in the Bioself memory have been transmitted to the Bioself center.

The information will be printed out in chronological order in the form of diagrams, which the Bioself center will send you, by post, fax or e-mail, as you prefer

Bioself – sub-menus

The device has several menus allowing you to review stored data or *to modify certain parameters, such as:*

- Consult back-data on temperatures and the length of cycles;
- Modify the time zone of temperature recordings;
- Transmission of stored data to a Bioself center;
- Choice of the acoustical morning reminder;
- Choice of temperatures in °C or °F;
- Correction of the starting date of the new cycle.

All these menus are shown in detail in the instruction manual that comes with every Bioself.

Bioself - reputation and standing

Bioself is the most reliable and easiest-to-use fertility indicator, according to a study conducted in Germany ("Neue Technologien in der Familienplanung", Maltser Werke, Kalket Haupstrasse 22-24, D-551103 Cologne)

Bioself *is a processor for temperature data and for the statistical* analysis of menstrual cycle duration. It is recommended by gynecologists interested in natural methods.

Bioself is a Class II medical instrument, developed and manufactured in Switzerland (Swiss Made label), which has been constantly improved and upgraded since its introduction.

Bioself bears the CE stamp (CE0459), and is certified ISO13485. It is approved by the American FDA (Food and Drug Administration, section 510k, registration N° 8030991). ISO 13485.

BIOSELF™
PO Box • CH-1226 THONEX-GENEVE
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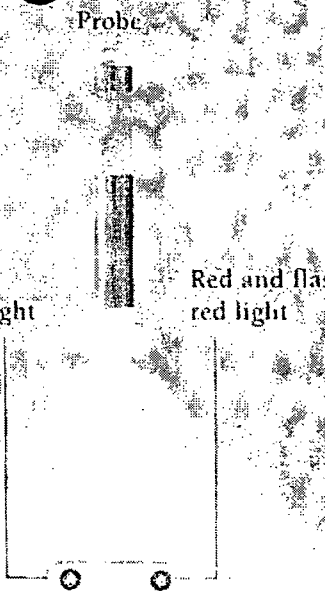


Display screen

Black button to access additional functions

Red menstruation button

Transmission speaker (on the back)

Battery compartment (on the back)

BIOSELF

BIOSELF

Fertility Indicator

WARNING

- BIOSELF® can be used by women who have menstrual cycles - preferably regular - lasting between 18 and 39 days.
- BIOSELF® should not be used while breast-feeding or using hormonal treatments (eg. the pill) or if you are aware of menopausal symptoms.
- BIOSELF® does not provide any protection against sexually transmitted diseases (AIDS, etc.).

CE 0459

Web site www.bioself.com
Email admin@bioself.com

Made in Switzerland

BIOSELF® SA
P.O. Box
CH-1226 THONEX-GENEVA
Tel. (41) 22 349 08 13 Fax (41) 22 348 12 11

Rev. 02-2003

If that is your question...

...BIOSELF® had you in mind when it developed a safe, alternative natural family planning method, without side effects

BIOSELF®

BIOSELF® is a simple, quick and accurate electronic fertility indicator. It is a step forward in the area of natural family planning, because it identifies both the period of maximum fertility (the days on which it is most likely you could conceive a child) and the infertile period, when conception is not possible (during which there is no need to use a barrier contraceptive).

Well-know principles

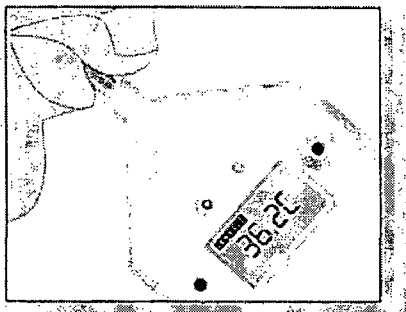
The BIOSELF® high-power micro-computer combines the basal body temperature and the calendar method. Through the latest developments in microelectronics, BIOSELF® render these natural methods both reliable and easy to practice.

BIOSELF® records and analyses your basal body temperature, and the length of your cycles, to keep you posted, at all times, on your daily level of fertility. It stores all the data, relating to your last 12 cycles, and becomes personalized to you as you use it.

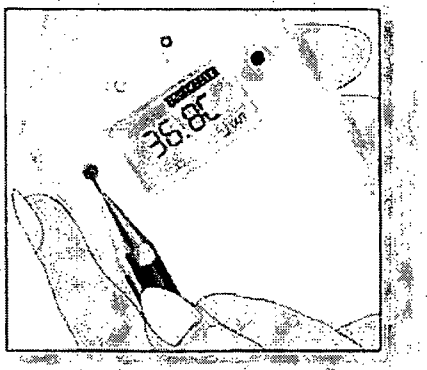
BIOSELF® also allows you to have the sequence of your cycles printed out in the form of a graph.

Easy to use

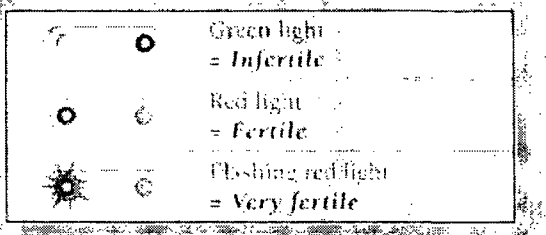
BIOSELF® is very simple to use. Every morning, when you wake up, at about the same time, it takes only a few moments to measure your basal body temperature. BIOSELF® even prompts you with a discrete audible signal, so that you do not forget.



Once a month, on the first day of your period, you press the red button, to record the start of your new cycle in the BIOSELF's memory.

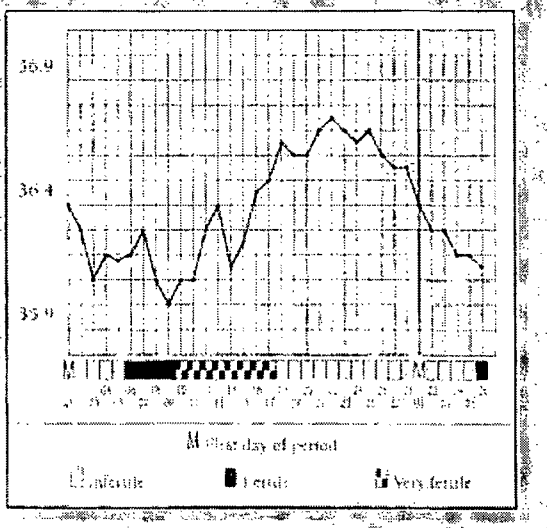


After automatically analyzing and processing this information, BIOSELF® uses one of its indicator lights to tell you your fertility level for that day.



Printing out your graph

You can have the entire record of your menstrual cycles printed out as a graph by telephone.



This information may be very useful for your doctor, especially if you have any fertility problems, or to find out your likely delivery date after you have become pregnant.

BIOSELF

BIOSELF

COVER SHEET MEMORANDUM

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

From: Reviewer Name Yun-shang Piao

Subject: 510(k) Number K122337/S002

To: The Record

Please list CTS decision code: SE - Substantially Equivalent

☐ Refused to Accept (Note: this is considered the first review cycle. See screening checklist.)

☐ Hold (Additional Information or Telephone Hold)

☒ Final Decision (SE, SE with Limitations, NSE (select code below), Withdrawn, etc.)

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 or 510(k) Statement *(Attach Summary or Statement)*	X	
Truthful and Accurate Statement *(Must be present for a Final Decision)*	X	
Is the device Class III?		X
›es firm reference standards? (If yes, please attach Form 3654.)	X	
Is this a combination product?		X
Is this a reprocessed single use device? (See Guidance for Industry and FDA Staff - MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices.)		X
Is this device intended for pediatric use only?		X
Is this a prescription device? (If both prescription & OTC, check both boxes.)		X
Is clinical data necessary to support the review of this 510(k)?		X
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 was incomplete, then applicant must be contacted to obtain completed form.)	X	
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 to < 2 years)		X
Child (2 years to <12 years)		X
Adolescent (12 years to <18 years)		X
·ansitional Adolescent A (18 years to <21 years); Special considerations are being given to this group, different from Jults age >= 21 (different device design or tesating, different protocol procedures, etc.)		X
Transitional Adolescent B (18 years to <21 years); No special considerations compared to adults >= 21 years)		X

Nanotechnology		X
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance)		X

Regulation Number:	None
Class:	Unclassified
Product Code:	LHD
Additional Product Codes:	

Digital Signature Concurrence Table
(Not all signatures may be required)

Branch Chief Sign-Off	Elaine Blyskun -S 2013.08.06 15:52:50 -04'00'
Division Sign-Off	Glenn B. Bell -S 2013.08.06 16:34:19 -04'00'

K122337 /SOD

fertility focus

March 19, 2013

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to FDA Questions to K122337
OvuSense Advanced Fertility Monitoring System

Dear (b)(4)

Fertility Focus hereby submits additional clarification and documentation in support of the OvuSense K122337 under your review. We are addressing your questions dated October 5, 2012. Two paper copies and one eCopy were sent to the FDA Document Mail Center. The eCopy is an exact duplicate of the paper copy except the eCopy also contains raw data (Zip files) in the STATISTICAL DATA folder.

Your questions are in bold and Fertility Focus answers are in regular type face. Where a response includes an attachment, the attachment is labeled according to the question number. For example, Attachment Q3-1 would be Question 3 attachment 1.

Fertility Focus regards information provided in support of this Traditional 510(k) to be confidential and proprietary and afforded such protection under 21CFR 807.95 and other applicable statutes. We understand that the submission to the government of false information is prohibited by 18 U.S.C. 1001 and 21 U.S.C. 331(q). In accordance with the Safe Medical Devices Act of 1990, a 510(k) Summary of Safety and Effectiveness is included in this notification. A Premarket Notification Truthful and Accurate Statement has also been provided in this submission in accordance with 21 CFR 807.87(j).

We trust this additional clarification meets your needs to complete the review of the Fertility Focus 510(k) K122337. If there are any questions, please contact me at 678-428-6978 (phone) or email to pennynorthcutt@theregsolutions.com for interactive review.

Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

43

March 19, 2013

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to FDA Questions to K122337
OvuSense Advanced Fertility Monitoring System

Dear Dr. Luo:

Fertility Focus hereby submits additional clarification and documentation in support of the OvuSense K122337 under your review. We are addressing your questions dated October 5, 2012. Two paper copies and one eCopy were sent to the FDA Document Mail Center. The eCopy is an exact duplicate of the paper copy except the eCopy also contains raw data (Zip files) in the STATISTICAL DATA folder.

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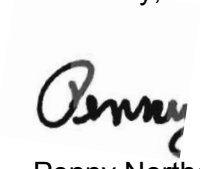
Sincerely,



Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

RESPONSE TO FDA QUESTIONS OF OCTOBER 5, 2012
OVUSENSE ADVANCED FERTILITY MONITORING SYSTEM

CONTENTS

Page No.

TABLES

FIGURES

FDA reviewer, Michele Lou, expressed risk vs. benefit questions in a phone conversation of Nov 30, 2012. Fertility Focus is providing a Clinical Risk vs. Benefit discussion below.

It is important for FDA to reread Section 3.1 Clinical Need in the original submission please. We will not reiterate it here.

For women wanting a family and having difficulty becoming pregnant, detecting the time at which they ovulate each month and predicting their most fertile period has potentially significant benefit, although other factors may affect the ability to conceive (see original submission Attachment M section 1.1.). OvuSense was developed to give women an easy, stress free method to detect and chart the timing of ovulation and the window of optimum fertility each month, and thereby improve quality of life for women having problems conceiving.

Subsequent to the original submission, a number of clinical papers have been prepared by the team involved in the OvuSense Trial conducted in (b)(4) [redacted] and described in attachment M – OvuSense Clinical Investigation Plan in the original submission. These build on the analyses presented in attachment R - OvuSense Clinical Investigation Study Report of the original submission. One of these papers has been published,[1] the second has been accepted for publication and is under second revision,[2] and the final paper is in preparation. Analysis from these new papers is included in the summary below, and in the answers to Q19 and Q20.

How well is the medical need this device addresses being met by currently available therapies ?

There is significant research evidence (see original submission Section 3.1 and Attachment A - Literature References) which demonstrate that temperature is an effective indicator of ovulation in women. By measuring core body temperature overnight with (b)(4) [redacted], in a site closest to the temperature rise associated with ovulation and free from external influences, this device can establish a highly accurate picture of average basal temperature on a nightly basis. By monitoring and logging this average temperature over a woman's complete monthly cycle, OvuSense can more accurately detect the day of ovulation, or the absence of ovulation in a particular cycle and predict her window of maximum fertility for the following cycle.

The OvuSense device is not the first device to use body temperature to predict ovulation. The Bioself 2000, predicate device, also measures basal body temperature via vaginal (or oral) temperature measurements, but with only one reading each morning. OvuSense also uses basal body temperature, and vaginal measurement, but calculates the temperature using a large number of nightly readings.

OvuSense provides accurate readings because:

- The measuring site, the vagina, is much closer to the site of thermogenic action of progesterone on the ovary – i.e. the site where the temperature rise associated with ovulation occurs – than alternative oral temperature based methods.
- It measures overnight when the body temperature is at its most stable.

[1] Papaioannou,S., Aslam, M., Ovulation Assessment By Vaginal Temperature Analysis (The Ovusense Advanced Fertility Monitoring System) In Comparison To Oral Temperature Recording, San Diego - United States of America: American Society for Reproductive Medicine 68th Annual conference, 2012.
[2] Papaioannou,S., Aslam, M., User's acceptability of Ovusense: a novel vaginal temperature sensor for prediction of the fertile period. Am J Obstet Gynecol, 2012. Under second revision.

- The temperature sensor has a measurement resolution of (b)(4) [redacted]
- Multiple readings and filtering create a highly accurate representation of the lowest (basal) temperature.

Alternate BBT devices are traditional thermometers. Traditional oral basal body temperature measurement has inherent inaccuracy; it is a measurement significantly influenced by external variances, with no repetitions to smooth out bias and using a technology which itself has limited measurement accuracy (even modern digital oral thermometers are only able to distinguish gradations of 0.01 °C). In addition, charting of oral temperature is deemed as inconvenient by users due to manual input and having to keep a diary of readings.

More modern surface thermometers which take multiple readings with a more accurate measuring technology are still unable to eliminate the inherent problem with measuring a surface temperature. Namely; the body regulates internal temperature by actively changing the surface temperature, often in opposition, thus the surface cools in order that internal temperature can rise, and vice versa. Measurements at the skin surface and orifices close to the surface are therefore prone to bias and are unable to represent a truly accurate picture of temperature rises associated with ovulatory activity.

The other main personal diagnostic used is urine luteinizing hormone (LH) strips. The luteinizing hormone surge happens just prior to ovulation. The use of LH strips is deemed inconvenient by users as relying on spot testing requires the use of two strips every day throughout the cycle to create a sufficiently accurate picture, with only a positive result showing ovulation is just about to occur. As will be discussed below, this information is anyway too late in the fertile window to maximize the chances of conception.

Traditional thinking about predicting the potential fertile days is based on two assumptions;

1. That ovulation consistently occurs 14 days before the start of the next period for all women
2. That women are fertile for several days before as well as after ovulation.

It follows then that in the textbook cycle length of 28 days, the fertile days should consistently be expected between cycle days 10 and 17.

However, these assumptions are outdated and are now shown by the contemporary scientific literature to be incorrect. Firstly, it is improbable that the reproductive function of billions of women of different body size, reproductive age, environmental conditions etc, can be adequately described by such simplistic, basic, universal assumptions. We now also know that only a small percentage of women ovulate exactly 14 days before the onset of menses,[3, 4, 5] this being the case even for women who usually experience a 28 day cycle length.

[3] Baird, D.D., McConnaughey, D.R., Application of a method for estimating day of ovulation using urinary estrogen and progesterone metabolites. Epidemiology, 1995. 6(5):547-550.
[4] Lenton, E.A., Landgren, B.M., Normal variation in the length of the luteal phase of the menstrual cycle: identification of the short luteal phase. Br J Obste Gynaecol, 1984. 91(7):685-689.
[5] Lenton, E.A., Landgren, B.M., Normal variation in the length of the follicular phase of the menstrual cycle: effect of chronological age. Br J Obste Gynaecol, 1984. 91(7):681-684.

Wilcox and colleagues demonstrated that in only approximately 30% of women is the fertile window entirely between cycle days 10 and 17. Most women reach their fertile window earlier and some much later.[6] They go on to recommend that women should be advised that the timing of their fertile window can be highly unpredictable, even if their cycles are usually regular, advice also reflected in an American Society of Reproductive Medicine Committee opinion paper on optimizing natural fertility.[7]

Similarly, the perception that the possibility of conception remains high after ovulation has occurred is not supported by data. The fertile window, approximately seven days long, practically ends on the day of ovulation; intercourse within the earlier stages of this time window, and particularly on the two days immediately before ovulation, is most likely to lead to conception, as demonstrated by extensive population data collected by Colombo and Masarotto[8], amongst others.[9,10]

Therefore, it makes sense that methods that prospectively identify the complete window of maximum fertility (the fertile period), are of much more potential use in optimizing the timing of conception than those which rely on LH surge within the current cycle, especially when this prediction can adapt to the woman's individual cycle pattern. This is especially important for busy modern couples. Intercourse during the fertile period has been reported to reduce the time to conception.[11]

The results of the OvuSense Trial described in attachment M – OvuSense Clinical Investigation Plan in the original submission and clinical benefits are further covered in the responses to questions 19 and 20 in this document.

Do the probable benefits outweigh the probable risks?
The device provides users with much more accurate information about the timing of their ovulation and identifies their most fertile period for the following cycle. This enables them to time their sexual intercourse to improve their chances of conceiving. There is both anecdotal and research evidence referenced by ASRM[7] which shows the high levels of anxiety from which women suffer when having difficulty in conceiving, and in using devices which detect the day of ovulation during the cycle. OvuSense can assist with reducing this stress by allowing careful advance timing of conception using the fertile period prediction.

[6] Wilcox, A.J., Dunson, D., The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ, 2000. 321(7271):1259-1262.
[7] American Society for Reproductive Medicine (ASRM), Optimizing natural fertility. Fertil Steril, 2008. 90(5 Suppl) S1-S6. No reprints available; available online at: www.sart.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Committee_Opinions/optimizing_natural_fertility(2).pdf
[8] Colombo, B., Masarotto, G., Daily fecundability: First results from a new data base. Demogr. Res, 2000. 3:article 5.
[9] Dunson, D.B., Baird, D.D., Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation. Hum Reprod,1999. 14(7):1835-1839.
[10] Wilcox et al 2000
[11] Frank-Herrmann, P., Gnoth, C., Determination of the fertile window: reproductive competence of women--European cycle databases. Gynecol Endocrinol, 2005. 20(6):305-312.

Although there are risks associated with the device, these would be well understood by users via the Users Operating Manual. Tampons are now in extensive use and their risks are clear. Risks associated with the OvuSense Sensor are similar. There is a very low risk of harmful events, and none have taken place in use. Most people using mobile phones or other similar portable electronic devices using chargers are aware of electrical safety risks arising from their use and precautions with use.

Are patients willing to take the risk of this treatment to achieve the benefit?
Yes. Risks are low (no adverse events were located in MAUDE database nor were any experienced in the clinical study). Risks are outweighed by benefits associated with increased chances of conceiving. Risks are mitigated by way of passing electrical testing, biocompatibility testing and a validated User Manual and labeling. The device is removable, it is checked daily by the user, the HFE validation confirms that the user manual provides adequate levels of instructions and any potential adverse events are well understood and made clear. Papaioannou[12] shows the high acceptance, comfort and ease of use associated with the device during the OvuSense Trial.

Summary of the Benefit(s)
The principal benefit allows users, who are seeking to conceive and have been unable so to do, to identify, more accurately than has been previously possible, the timing of their ovulation each cycle, and their most fertile period for the following cycle. This should reduce the stress associated with conception, help discover potential issues associated with the cycle, and for those with regular ovulation improve their chances of becoming pregnant.

Summary of the Risk(s)
The principal critical/serious risks listed in the Risk Assessment Matrix (see response to Question 10 and 11 and section 5.3 of the original submission) are associated with toxicity arising from the Sensor in position and electrical failures of the Reader and Sensor, when the latter is not in place.

The Sensor has been assessed for biocompatibility following guidance in ISO 10993, and further FDA requirements, and has passed satisfactorily. The OvuSense Reader and Sensor comply with IEC 60601-1, thus largely eliminating electrical safety risks. There is a critical risk associated with leaving the device in place during sexual intercourse, but this is a clear misuse of the device. All other risks are minor or negligible.

Final Validation of Benefit through successful Clinical Studies
The conclusion of the clinical study proved the hypothesis “That the AFMS system would be a more accurate instrument in the detection of ovulation than the traditional oral temperature recordings chart.” The results proved the hypothesis to be correct at a very high level of statistical significance and to a degree that suggests the shortcomings of oral temperature measurement identification of ovulation are overcome.

Clinical References
See **Attachment CRBR-2** for copies of the clinical papers cited in this section.

[12] Papaioannou,S., Aslam, M., User's acceptability of Ovusense: a novel vaginal temperature sensor for prediction of the fertile period. Am J Obstet Gynecol, 2012. Under second revision.

1. **Please revise your Indications for Use to include all versions of the devices (e.g, personal sensor only, reader only, starter pack) in the device name. Please modify the Indications for Use form, 510(k) Summary, and device labeling accordingly.**

There are several requests for additional information from the FDA regarding device models. For clarification, there is only one model or version of the device, Model # M009-US for the Starter Kit which includes both a Reader, Model # M010-US, and a Personal Sensor, Model # M011, and only one device name, OvuSense Advanced Fertility Monitoring System. This version was designed and tested with a white color sensor. No other colors are offered. See Q3 for details on colorant.

Fertility Focus has revised the following documents as you requested.

See **Attachment Q1-1** for a revised Indication for Use Form.

See **Attachment Q1-2** for a revised 510(k) Summary.

See **Attachment Q1-3** for revised OvuSense User Manual which includes device model number and reorder numbers.

2. Please revise the 510(k) Summary and include the following information as required per 21 CFR 807.92:

a. Provide a separate 510(k) Summary that clearly states "510(k) Summary" on the top of the first page;

b. Update the Indication for Use shown to be identical to that requested in Deficiency No.1 above;

c. Describe in more detail the performance characteristics of the device, i.e., how the device functions;

d. Provide a detailed comparison of the technological characteristics of the subject and predicate devices and justify any differences;

e. Describe the performance testing conducted on the subject device in greater detail, including electrical testing, biocompatibility testing, bench testing, and clinical validation testing.

Please note that we may request additional changes to your 510(k) Summary as we continue our review of your file.

See **Attachment Q1-2** for a revised 510(k) Summary. The Summary has been updated to include the following:

a. We have provided a separate 510(k) Summary that clearly states “510(k) Summary” on the first page
b. We have updated the indications for use to match the revised Indications for Use form in Q1-1 attachment
c. We have updated the “Description of the Device” which discussed how the device functions in the 510(k) Summary
d. We have provided a detailed comparison of technological characteristics of the OvuSense and the predicate device under “Technological Characteristics” in the 510(k) Summary
e. Details of performance testing of the device including electrical testing, biocompatibility testing, bench testing, and clinical validation testing have been completed in the 510K Summary with greater detail.

3. You did not provide sufficient information on device materials. Please provide a table summarizing each component used in the device, including the materials, the additives used (e.g., colorant) and their final concentrations (w/w), and the function of each component. In addition, please provide detailed information on each component (e.g., product name, CAS number, supplier, catalog number, Certificate of Analysis, Material Safety Data Sheet, etc.).

In FDA's Additional Information letter, there are several questions regarding device models/colorants. For clarification, there is only one model or version of the device, Model # M009-US for the Starter Kit which includes both a Reader, Model # M010-US, and a Personal Sensor, Model # M011, and only one device name, OvuSense Advanced Fertility Monitoring System. This version was designed and tested with a white color sensor. No other colors are offered. Material information was submitted in the original submission including MSDS and supplier information. However to accommodate FDA request, Fertility Focus has supplied as much information as was possible to obtain from the supplier.

See table below summarizing each component used in the device including the materials, the additives used (e.g., colorant) and their final concentrations (w/w), and the function of each component.

Table Q3-1 provides details on Personal Sensor materials. Table Q3-2 that follows provides details on Reader materials.

See **Attachment Q3-1** for Personal Sensor materials information and Material Safety Data Sheets.

Table Q3-1: Personal Sensor Materials

Function	Material	CAS No	% Used	Supplier/Part No./ Supplier Cat No	Patient Contacting (YES or NO)
(b)(4)					

Table Q3-1: Personal Sensor Materials					
Function	**Material**	**CAS No**	**% Used**	**Supplier/Part No./ Supplier Cat No**	**Patient Contacting (YES or NO)**
(b)(4)					

See **Attachment Q3-2** for Reader materials information and Material Safety Data Sheets. Table Q3-2 details the Fertility Focus materials as FDA requested. These materials are NOT PATIENT CONTACTING.

Table Q3-2: Reader Materials

Component	Material	CAS No	% used	Supplier/Part No.//Supplier Cat No	C of A Ref	MSDS Ref	Patient Contacting (YES or NO)
(b)(4)							

Table Q3-2: Reader Materials							
Component	**Material**	**CAS No**	**% used**	**Supplier/Part No.//Supplier Cat No**	**C of A Ref**	**MSDS Ref**	**Patient Contacting (YES or NO)**
(b)(4)							

Table Q3-2: Reader Materials							
Component	**Component**	**Component**	**Component**	**Component**	**Component**	**Component**	**Component**
(b)(4)							

4. You indicated that the personal sensor is colored with a series of color masterbatches. Please work with the supplier to provide the following additional information:

a. Purity level of colorant

b. Estimated absolute amount of colorant (in weight) per device

c. Identification of other US legally marketed medical devices by device name, manufacturer, submission number, where the colorants have been previously used, if known

d. Toxicity risk assessment of this colorant that is preferably (b)(4) [redacted]

e. (b)(4) [redacted] **(if known)**

This is a misunderstanding of our original submission. The Personal Sensor has only one colorant – white, and no other colorant or series of colors are available in this device. Sorry for the confusion.

a. The colorant is of medical grade manufactured by (b)(4) that is used in many other FDA cleared marketed medical devices. Due to (b)(4) [redacted], information for devices that are 510K cleared using this colorant are proprietary to Nusil and not available to Fertility Focus. Master Access File (MAF) for the colorant masterbatches has been filed with the USA Food and Drug Administration. (b)(4) [redacted]

b. The colorant (b)(4) [redacted]

c. Refer to answer to question 4a. above

d. There is no toxicity risk in the colorant. Appropriate biocompatibility testing has been conducted as below on the final finished devices with no toxicity risks identified. All biocompatibility testing passed. See additional biocompatibility testing results presented in Question 16.

- (b)(4) [redacted]

- (b)(4) [redacted])

e. It is unknown if this colorant is subject to a specific FDA regulation. See MAF reference in **Attachment Q4-1**.

5. Your device description indicates that both the personal sensor and the reader have rechargeable batteries. Please provide more information on both sets of batteries (type, rated voltage, and capacity in mAH). Please clarify whether the charging that occurs (and the battery charge indicator) applies to both batteries or just the batteries in the reader.

The Personal Sensor is sealed for life, contains a non-rechargeable battery and is not serviceable. The Sensor battery is (b)(4) [redacted]

The Reader contains a re-chargeable battery pack (b)(4) [redacted]

6. Please identify how the batteries are accessed. Explain how you keep the user from accessing the batteries.

The battery for the Personal Sensor is permanently sealed (see materials Q3) and is not accessible by the user.

The Reader battery is a re-chargeable pack situated within the secured unit. However, the Reader battery pack can be accessed by removal of the enclosure base. The enclosure base is secured by four tamper-proof screws. Two screws are located beneath the central rubber foot which is glued in place.

It is not intended for the user to access the battery. The user is warned, see page 3 of User Manual not to access the OvuSense Reader battery and this warning is clearly highlighted in the warning section of the "Electrical Safety & Compliance" of the User Manual **Attachment Q1-3**.

7. You indicated that the vaginal personal sensor measures and records BBT data and transfers data to the reader via an electromagnetic induction link. It is not clear how the data is processed. You mentioned that BBT data is measured in (b)(4) therefore multiple data points are collected each night. It appears that the graphs and other data presented to the user include one BBT data point per night. It is not clear how this data point is derived. Please explain how this is done. Further, please provide information on how fertile days are derived from the data.

A detailed description of the method by which raw data collected by the Sensor are processed in the Reader is given in the document **Attachment Q7-1** Summary OvuSense Performance Characteristics & Functionality including Algorithm. (b)(4)

8. Further, explain whether any data is considered unusable, such as too low, too high, etc. How is this data handled? How are the data calculated when values are unusable or missing?

The filtering of the complete data for a single night is described in Section 16.2 of **Attachment Q7-1** "Summary OvuSense Performance Characteristics & Functionality including Algorithm".

In summary, (b)(4) [redacted]

The filtering of the derived single point reading representing overnight temperature for determination of date of ovulation are described in Section 16.5.1 of **Attachment Q7-1** "Summary OvuSense Performance Characteristics & Functionality including Algorithm".

In summary, (b)(4) [redacted]

9. We were unable to locate an adequate description of the software algorithm for OvuSense in your submission. Therefore, it is unclear how the OvuSense software uses the data collected from the Personal Sensor to calculate/estimate the day of ovulation. Other details of the software algorithm are also unclear, such as whether the software adjusts the algorithm as data on multiple cycles from a user accumulates. Please provide a clear description of the OvuSense software and how it uses data on continuous resting nocturnal vaginal temperature measurements to estimate the day of ovulation. Please also explain whether or not data from multiple cycles is used to adjust the estimate of the date of ovulation.

These questions all relate to the method for calculating the fertile period.

The descriptions you request are contained within the document **Attachment Q7-1** "Summary OvuSense Performance Characteristics & Functionality including Algorithm". The software and usage is described in Sections 6-15, and the algorithm is described in detail in Section 16.

Section 16.5 describes how the OvuSense software uses the data collected from the Personal Sensor to calculate/estimate the day of ovulation.

(b)(4) [redacted]

[redacted]

This is because the averaging of multiple cycles of data is unlikely to provide useful predictive information. Generally speaking, as can be read in the information supplied in other sections of this document, women who do not ovulate on the expected "middle of the month" norm,

(b)(4) [redacted] A woman with chaotic ovulation would not be helped by an algorithm which averaged out the day of ovulation in multiple cycles. (b)(4) [redacted]

(b)(4) [redacted]

10. Your Hazard analysis indicates compliance of the battery charger with EN 60601-1 for mitigation of Energy Hazards (electric shock, burn, fire). However, this only ensures that the charger safely provides the power and/or trickle charge in a safe way; i.e., that the charger is electrically safe. This does not ensure that the entire device is electrically safe. Please revise your Hazard analysis to reflect all mitigations to address electrical shock, burn, fire, explosion, and battery leakage. Also address both sensor and reader interface with the user.

The hazard analysis, called Risk Assessment Matrix by Fertility Focus, submitted in Section 5 Table 5.3 in the original 510K submission, did include electrical shock, burn and fire. This risk assessment has been updated to reflect all mitigations to address electrical shock, burn, fire, and it now includes explosion and battery leakage. Fertility Focus risk assessment addresses both Sensor and Reader interface with the user. No unacceptable risks remained following mitigation. All risks that remained in the ALARP region were considered to have an extremely low probability of occurrence. See original submission, Section 5, Summary of Risk.

See **Attachment Q10-1** for updated Risk Assessment Matrix.

11. Your document titled "System Acceptance Test & Trace Specification" is identified as fulfilling the requirement for a traceability analysis/matrix document. This document includes a table that provide a requirement identification number (format xxx_xxx_###) and identification of the corresponding test number (format test##).

However, this document does not include any reference to hazards. Further, the hazard analysis does not appear to include reference to requirements or software tests. The reference number included in the hazard analysis chart uses a format (x.x) that does not correspond to any numbers we can identify. Also, no test ID numbers are included Thus, the hazards are not tied to tests in the hazard analysis or the traceability analysis.

While we understand that not all hazards will have a correlating software test, the functional failure hazards should include some software testing (specifically identified). All or most of the hazards should have a correlation to the requirements. Please explain where this is provided in the documentation we have or provide an additional document that shows correspondence between all of the following: requirements, testing, and hazards.

The software development and release are controlled by the Risk Management process. See **Attachment Q10-1** for updated Risk Assessment Matrix.

See **Attachment Q11-1** for Fertility Focus risk documents, specifically Risk Management Plan, Hazard Identification, and Risk Management Report developed in compliance with ISO 14971 Application of risk management to medical devices.

See **Attachment Q11-2** for a Software Traceability Matrix that cross-references software testing to the requirements and shows how functional failure hazards have been tested.

12. Your software revision level history only indicates that the current version is version 1.3. Please identify previous versions (developmental versions) and a brief description of difference with each version.

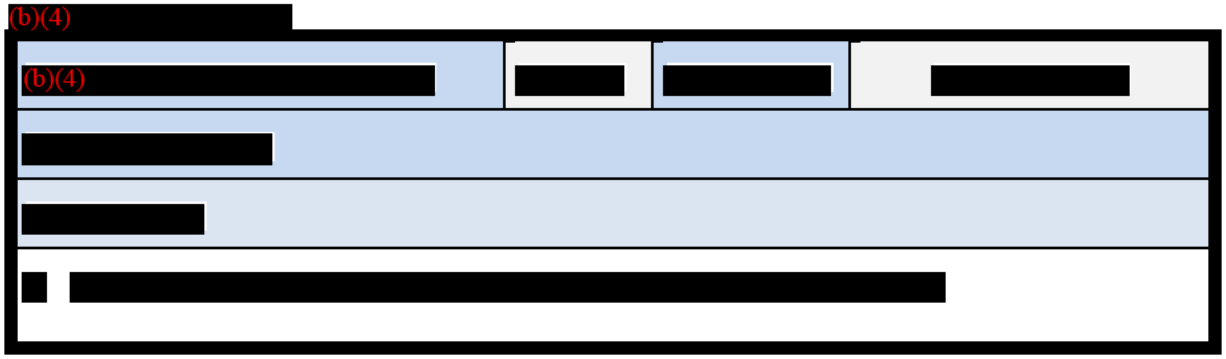
Section 5.7, page 62, of the original 510K submission correctly identified the **current release software version as 1.3**, released 24 January 2012. See the release charts below. Notice Release ID: OSR_1_3.

The software release notes supplied at each release identify the changes as listed below.

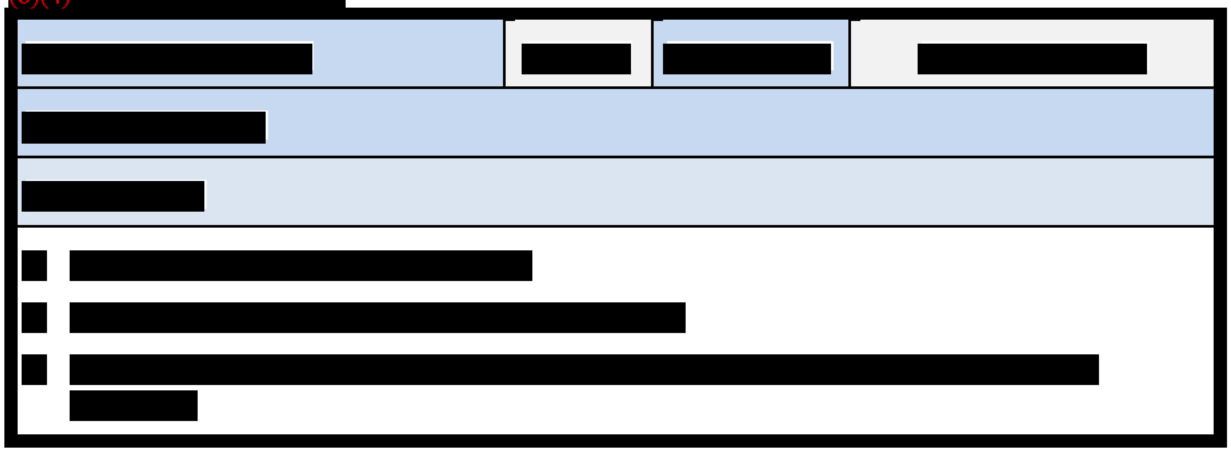
The software algorithm has not changed since the initial production software release/build which was used in the clinical trial.

There are not any known bugs or anomalies present within the OvuSense Advanced Fertility Monitoring System software release: software (b)(4)

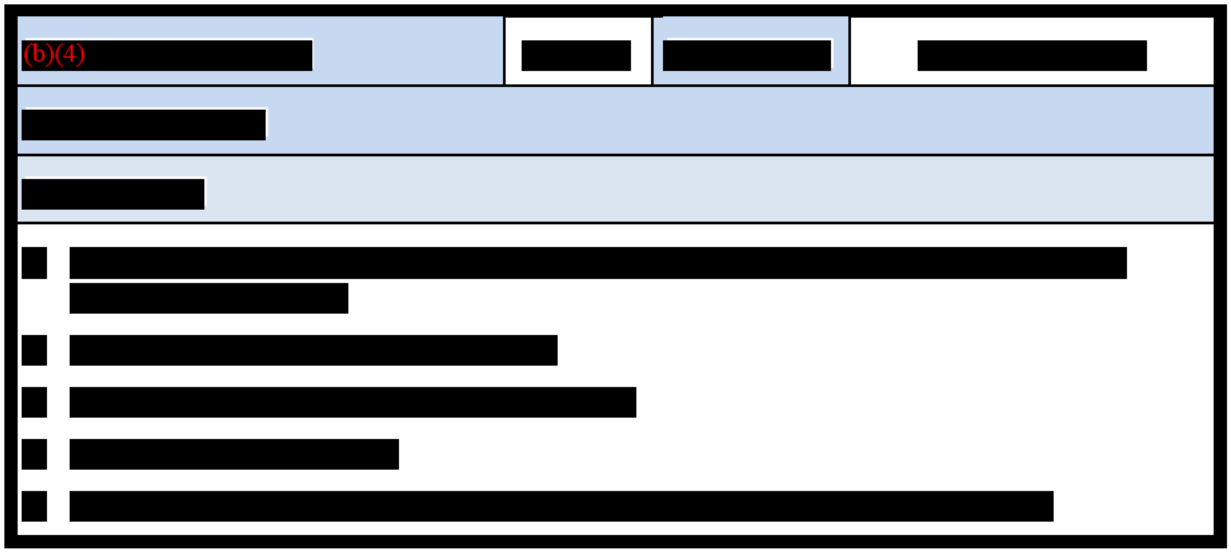
(b)(4)



(b)(4)

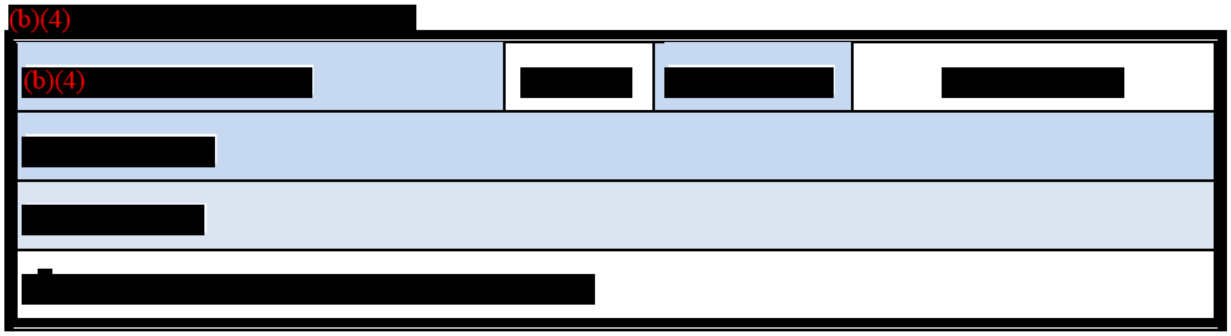


PRODUCTION VERSION



(b)(4)

(b)(4)



PRE-PRODUCTION VERSION

SOFTWARE RELEASE ID:	a01a.d34	Release Date:	25 January 2008
Build ID: None			
Change Details			
Baseline software (pre-production)			

13. General safety testing (IEC 60601-1 report in attachment O) describes a power supply unit. Please explain whether the charger is a battery charger only or if it also serves as a power adapter for the reader.

The power supply unit both charges the battery and supplies operational power to the Reader.

See sections 4.10 and 4.11, in the original 510K submission, Attachment O, of the IEC 60601-1, TRA-004397-34-02A report regarding the safety of the power supply. All testing passed.

See **Attachment Q13-1**, a summary of EMC and Safety Testing.

14. Please explain why general safety testing occurs at 90 Vac and 264 Vac. How does this apply to use in the United States? Also how does this relate to use with a DC power supply or batteries?

Conducting tests at 90VAC and 264VAC, verifies safety of the power supply unit across its full specified operational range including 120VAC, which is USA mains supply. The power supply unit generates a stable 9VDC for the Reader, when connected to any AC power supply between 90VAC and 264VAC. The charger is fully compatible with all global mains voltages.

15. The general safety testing does not appear to fully address electrical shock or leakage current but merely identifies that the power supply is compliant. Please explain why compliance of the power supply with IEC 60601-1 ensures that your device, when connected to the power supply or to the batteries, will not in any way deliver energy (electrical, thermal, etc.) to the patient in a way that could result in injury. We understand that the supply voltage will be 9 volts or less, please include this in your discussion of the safety of the device.

The patient applied part (Personal Sensor) has no connection-terminal to the 9VDC power supply and hence to mains at any time. The Personal Sensor battery is not re-chargeable and also is not accessible to the user. (b)(4) [redacted].

The downloading of data from the Personal Sensor is accomplished using a contactless RF link when the Personal Sensor is placed onto the Reader. At this point the user does not have contact with the unit.

Both the Reader and Personal Sensor devices are constructed of fully insulative materials. Neither the Personal Sensor nor the Reader contain any harmful voltages.

16. (b)(4) [redacted] testing was included in your submission to support the biocompatibility of the patient contacting portions of your proposed device. The test methods identified would be supportive of a device with limited contact with mucosal tissues. However, the proposed device will be used daily for up to 21 days per month and may be used for many months. Therefore, this device could be considered a permanent implant in contact with mucosal tissue. Per FDA Bluebook memo G95-1, testing to support long-term use of the device would include (b)(4) [redacted] Alternatively, you may also identify other 510(k)-cleared devices using the (b)(4) [redacted] A second alternative would be to provide a detailed toxicological risk assessment for the (b)(4) [redacted] assessment of exposure risk to chemicals liberated for the device (e,g., potential to elicit (b)(4) [redacted]

In FDA's Additional Information letter, there are several questions regarding device models/colorants. For clarification, there is only one model or version of the device, Model # M009-US for the Starter Kit which includes both a Reader, Model # M010-US, and a Personal Sensor, Model # M011, and only one device name, OvuSense Advanced Fertility Monitoring System. This version was designed and tested with a white color sensor. No other colors are offered. The Personal Sensor is not a permanent implant but used consecutively on a nightly basis.

(b)(4) [redacted]

- (b)(4) [redacted]
-
-
-
-
-

See **Attachment Q16-1** for biocompatibility test reports.

17. You indicated that the personal sensor is colored with a series of color "masterbatches." Please clarify if you plan to market one or multiple color versions of the sensor. If more than one color sensor is proposed, independent biocompatibility testing will be needed to support each color version proposed, unless you can show that the identical materials (supplier, catalog number, colorants, mold release agents, contact potential, etc.) have been used in a 510(k)-cleared device. (b)(4) [redacted]

Sorry for this misleading statement. The Personal Sensor is provided in only one color, white. Fertility Focus does not intend to market any other color version of the sensor.

Fertility Focus has conducted biocompatibility testing on final finished devices which contain this white color according to FDA request. See **Attachment Q16-1** for biocompatibility results. All testing passed indicating there is no toxic affect when in contact with the user.

Nusil has provided a MAF for FDA reference. See **Attachment Q4-1** for copies of MAF authorization letters.

See material listing and details in Table Q3-1: Personal Sensor Materials, and in Table Q3-2: Reader Materials. See **Attachment Q3-1** for Personal Sensor materials information and Material Safety Data Sheets. See **Attachment Q3-2** for Reader materials information and Material Safety Data Sheets.

18. Please provide mechanical testing to assess (b)(4) [redacted]

(b)(4) [redacted]

(b)(4) [redacted]

(b)(4)

[redacted]

(b)(4)

[redacted]

19. Of the three sections in your submission discussing the clinical validation study (Section 10, Attachment M and Attachment R), none explained how temperature measurements collected with the Personal Sensor were used to generate the estimated day of ovulation for comparison with the day of ovulation determined (b)(4) [redacted] (b)(4) [redacted]. The only actual data provided were (b)(4) [redacted]. No other information was provided to support the conclusion that the OvuSense predicted the day of ovulation with greater accuracy compared to the once-daily oral BBT. It is also concerning (b)(4) [redacted]). In order for FDA to independently verify your conclusion regarding the relative performance of OvuSense vs. oral BBT measurement, please provide all line data for each subject. Also, please provide a statement of your pre-specified statistical hypothesis test and definition of study success. (b)(4) [redacted].

Please see the introduction of this submission, Clinical Risk Benefit Analysis, for Fertility Focus conclusion that the OvuSense predicts the day of ovulation with greater accuracy compared to the once daily oral BBT.

Please see Fertility Focus response to FDA AI questions 7, 8, and 9 of this submission which deal with how the Reader estimates the day of ovulation from the data collected by the Sensor, for the ovulation (and hence fertile period) prediction by the software.

(b)(4) [redacted]

agreement with ultrasound folliculometry (US) when OvuSense measurement is used compared (b)(4) [redacted]

(b)(4) [redacted]

(b) [redacted]

(b)(4) [redacted]

* (b)(4) [redacted]

(b)(4) [redacted]

(b)(4) [redacted]

(b)(4)

[redacted]

20. Your study plan as described in Attachment M refers to Freundl *et al.* (2003) and Colombo and Masarotto (2000) as the basis for Study methodology for comparing the OvuSense vs. BBT. Freundl *el al.*'s (2003) study was designed to compare multiple methods for detecting the fertile period for contraceptive purposes, not for the purpose of becoming pregnant. Colombo and Masarotto (2000) produced a database of 7017 menstrual cycles contributed by 881 women to estimate daily fecundability. Colombo and Masarotto estimated the day of ovulation based on records of basal body temperature and mucus symptoms, not on ultrasound evidence, and therefore is subject to uncertainty. Please explain why you believe these two references are appropriate as the basis for the study design. Please also discuss whether it is necessary to cite these references in order to compare accuracy of OvuSense to BBT, using ultrasound evidence of ovulation as a gold standard to support the proposed Indication for Use.

As outlined in the response Q19, the method described by Freundl[15] which uses the Colombo and Masarotto[16] data is readily modified to accommodate comparison of devices to aid conception. This is because the identification of the fertile period is as relevant to conception as it is to contraception.

The method by which the Colombo and Masarotto results are derived is not relevant to the calculations from the Fertility Focus clinical data. Colombo and Masarotto is, however, relevant in indicating the importance of detecting the timing of ovulation and predicting the window of maximum fertility.

A number of methodologies may be used to compare the accuracy of OvuSense to BBT based upon an ultrasound gold standard reference.

The analysis of primary endpoint is presented in Section 4.1 of Attachment M – Clinical Investigation Plan in the original submission.

In Section 4.2 of the same Attachment M, Fertility Focus presented the difference between the two methods of detection by means (b)(4) as an additional analysis. The (b)(4)

In response Q19 of this submission, a further analysis by means of a (b)(4).

In addition, please see the Introduction of this submission, Clinical Risk Benefit Analysis, for Fertility Focus conclusion that the OvuSense predicts the day of ovulation (and hence fertile period) with greater accuracy compared to the once daily oral BBT.

The conclusions from these analyses, all derived from the results presented in the original submission, are consistent, and fully support the proposed indication for use.

[15] Freundl et al 2003
[16] Colombo et al 2000

21. It is unclear whether the OvuSense algorithm had been frozen prior to the validation study. In Section 6.5 of Human Factors Interface, you state that the results of (b)(4) [redacted].

The software algorithm in the device to be marketed is exactly the same as the one tested in the study. Yes the algorithm was frozen prior to the clinical validation study. No part of the algorithm was changed during the revisions of the software. The algorithm remained fixed throughout the clinical validation study. This same algorithm version will be the one released in the USA.

The changes which took place resulting from user feedback during the clinical validation study related to battery management and error handling. Neither of these software areas has an impact on results calculation and presentation. Please refer to release notes in response to Q12 of this submission.

Therefore the algorithm and thus the calculation and presentation of results to the user in the device to be marketed in the USA is exactly the same as in the product launched in Europe, and exactly the same as in the product tested in the clinical validation study.

22. The OvuSense is the first extended use vaginal probe for basal body temperature measurement. It is important, therefore, that you demonstrate the probe does not cause pain, discomfort, bleeding, etc. In Attachment R, you have stated “No adverse effects were reported” in the clinical validation study. Your submission does not describe, how safety was evaluated in the clinical validation study of the OvuSense. Please explain how safety information was obtained to support their conclusion.

Safety was assessed throughout the study. The study participants had 24 hours a day access to the consultant gynecologist responsible during this clinical trial and/or to the ultrasound scan clinic which acted as a central scanning clinic during the study. The patients were encouraged to report any problems to the consultant gynecologist or the ultrasound scan clinic. At no point in the trial, and despite the means available to trial participants, were any adverse events reported.

The consultant gynecologist responsible for the trial met with the women at the end of each cycle. Part of the purpose for this regular follow up was to specifically inquire for any adverse events. Despite the trial participants being specifically asked to report any such events, none did occur.

See **Attachment Q22-1** for a signed letter from the gynecologist responsible for the trial.

23. You have provided the primary and underside labeling for both the OvuSense Sensor and Reader in the submission. Please revise the labels as follows:
   a. Add storage conditions;
   b. Add lot number and expiration date;
   c. The label includes a number of unrecognized symbols; please add text directly next to each symbol on the primary and underside labels for both the OvuSense sensor and reader;
   d. Include the statement "THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE" to both labels.

Fertility Focus made the requested changes to labeling.

See **Attachment Q23-1** for revised Personal Sensor and Reader device labeling.

24. Please make following changes to the User Manual:

- **a. Add a separate Device Components Section at the beginning of the User Manual that lists all components of the device;**
- **b. Add a separate Warnings and Precautions Section at the beginning of the User Manual that includes Warnings and Precautions that are currently located throughout the User Manual;**
- **c. Please include the statement "THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE" in an individual text box in a prominent location on the front of the User Manual;**
- **d. Add a separate Direction for Use Section that instructs the user explicitly, step-by-step, how to operate the device that is currently located throughout the User Manual;**
- **e. On page 3 of the User Manual, you stated that the user could recycle the used reader and sensor. The sensor is a personal, single user device with a 3 month use life. The reader does not have an expiration date or use-life. Please state explicitly if the reader is a single user device and how long the use-life is;**
- **f. On page 6 of the User's Manual you stated that "If you do not have a regular cycle length, OvuSense may still provide you with information about your menstrual cycle and timing of ovulation." Please provide data to substantiate this claim, or remove this claim from device labeling;**
- **g. The personal sensor is an intra-vaginal, tampon-shaped device. On Page 13, you mentioned there may be a small risk of toxic shock syndrome, a rare condition caused by the growth of *Staphylococcus aureus* on blood or fluids in the vagina. Because the user may not be familiar with this medical emergency, please provide detailed explanation of the disease and include all warning signs. Please consider using the information from 21 CFR 801.430 (d), which is the regulation for menstrual tampon labeling;**
- **h. On Page 25, you stated that "the OvuSense Scales graphs using relative temperature points for each cycle." Please clarify what this means and how relative temperature points are related to the BBT;**
- **i. On Page 33, you stated that "if you experience... discomfort, irritation, or a vaginal discharge during use of the personal sensor, stop using the personal sensor immediately and consult your doctor." This statement seems to be contradicted to your statement of "No adverse effects were reported" in the clinical validation study. Please clarify the discrepancy;**
- **j. The label includes a number of unrecognized symbols; please add text directly next to each symbol used in the labels.**

Please note that we may identify additional labeling deficiencies following review of your updated labeling and your responses to the questions in this additional information letter.

In response to FDA comments see **Attachment Q1-3** for revised OvuSense User Guide and below responses.

- **a.** Page 1 now indicates device components.
- **b.** Page 1 and 2 now include a separate Warnings and Precautions Section.
- **c.** Page 1 now lists "This is not for Contraceptive Use" as do the device labels.

d. The new Directions for Use section begins on page 11.

e. Page 7 indicates this is a single user device. The revised reader label now includes an expiration date. See **Attachment Q23-1** for labels.

f. The claim has been removed.

g. See page 2 and 33 of User Manual with precautions for toxic shock syndrome.

h. On page 25 of User Manual, we stated that “the OvuSense Scales graphs using relative temperature points for each cycle.” This statement is now changed to, “Please note that for ease of viewing, OvuSense uses temperature graphs for each cycle, that are scaled relative to the highest and lowest temperature values achieved during the cycle.” See page 1 and 24 which relate to graphs.

i. On Page 32 of the User Manual, we stated that “if you experience... discomfort, irritation, or a vaginal discharge during use of the personal sensor, stop using the personal sensor immediately and consult your doctor.” This is precautionary text that should be included for any device of this nature. No adverse effects have been reported in the field, but if they should occur for whatever reason, the user should reasonably expect advice on what to do. We are of the opinion that removal of such a precaution would be contrary to our duty of care as a manufacturer. Do you agree?

j. See **Attachment Q23-1** for revised Personal Sensor and Reader device labeling, with text next to symbols.

25. Please provide Standards Data Report for 510(k) Forms (Form 3654) for all the standards you referenced to complete the performance testing requested in this review memo. You can access this from using the following link: http://www.fda.gov/downloadsfAboutFDAIRcportsMWIualsFormsiFormsfUCM081667.pdf.

(b)(4)

26. Your 510(k) did not include the Certification of Compliance with Requirements of the ClinicalTrials.gov Data Bank (Form 3674). Effective December 26, 2007, all firms submitting a 510(k) are required to submit Form 3674 regarding registration of applicable clinical trials in the Clinical Trials Data Bank (http://prsinfo.clinicaltrial.gov). Form 3674 can be obtained by going to the following web address: htm://www.fdagov/opacom/morechoices/fdaforms/FDA-3674.pdf. Please submit Form 3674 for review.

See **Attachment Q26-1** for the completed FDA 3674 form.

ATTACHMENT CRBR-1
ANALYSIS OF TEMPERATURE RESOLUTION

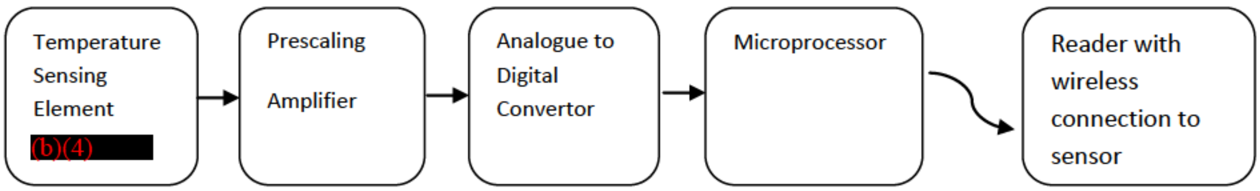
(b)(4) Analysis of temperature

Introduction

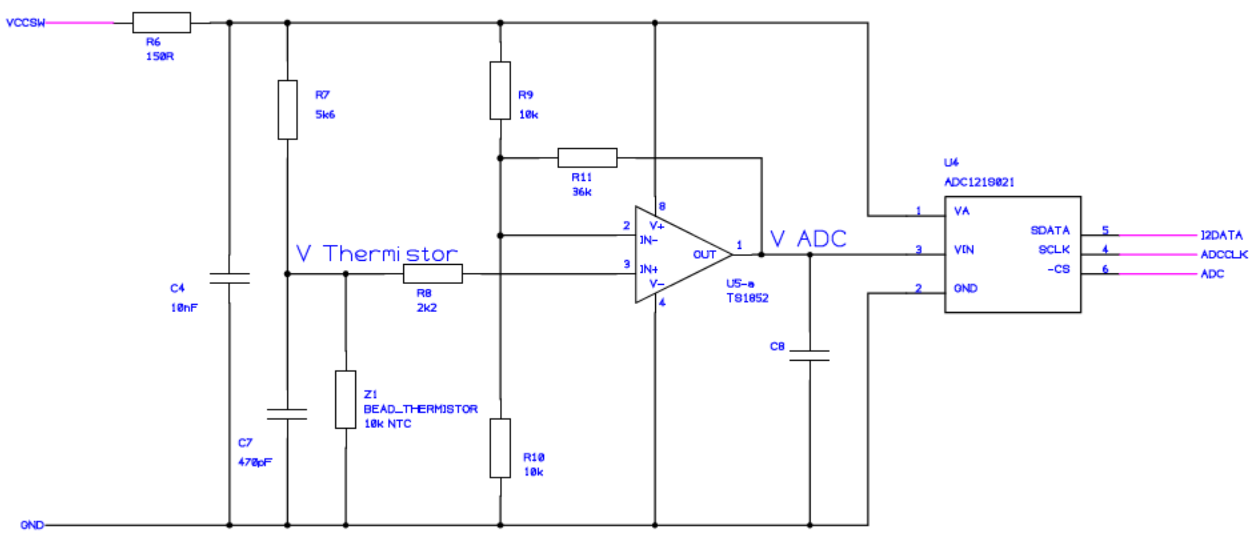
The Ovusense sensor is a wireless temperature monitor designed to detect small changes in body temperature at [redacted] The sensor connects wirelessly to a reader unit to download the recorded temperatures and display them to the user.

The purpose of this report is to analyse the temperature range and resolution of the sensor. In order for the device to perform its intended function it must be able to detect a change in temperature of 0.167°C but absolute temperature accuracy is not required.

The measurement is performed using a t[redacted]r and a preamplifier to generate a Voltage which varies with temperature. This is fed into an Analogue to Digital Convertor (ADC) connected to a small processor which stores the values until they can be transmitted to the reader.



Circuit description and analysis



The sensor uses a high accuracy Negative Temperature Coefficient (NTC)[redacted] (Z1) in conjunction with an operational amplifier based prescaler (U5) and a 12bit ADC (U4).

The (b)(4) is manufactured by Measurement Specialities under the Betatherm brand and has the model number Series VI 10K3A1AM. It is specifically designed for measuring body temperature and has a tolerance of +/- 0.05°C in the range 32°C—44°C.

Prescaling is achieved by a non-inverting amplifier is built around the ST TS1852 op-amp. This device is designed for low voltage circuitry and well suited to the application.

After the amplifier, the temperature dependant Voltage is fed into an ADC121S021 which is a 12 bit successive-approximation ADC from Texas Instruments. Based on a 3V supply, the least significant bit is thus 3V/4095 = 733µV.

Temperature readings are stored in the sensor as raw ADC data. Conversion from ADC readings to temperature is handled by a lookup/calibration table in the reader. The exact details are in the IPL source code which we have not been able to fully analyse.

Method

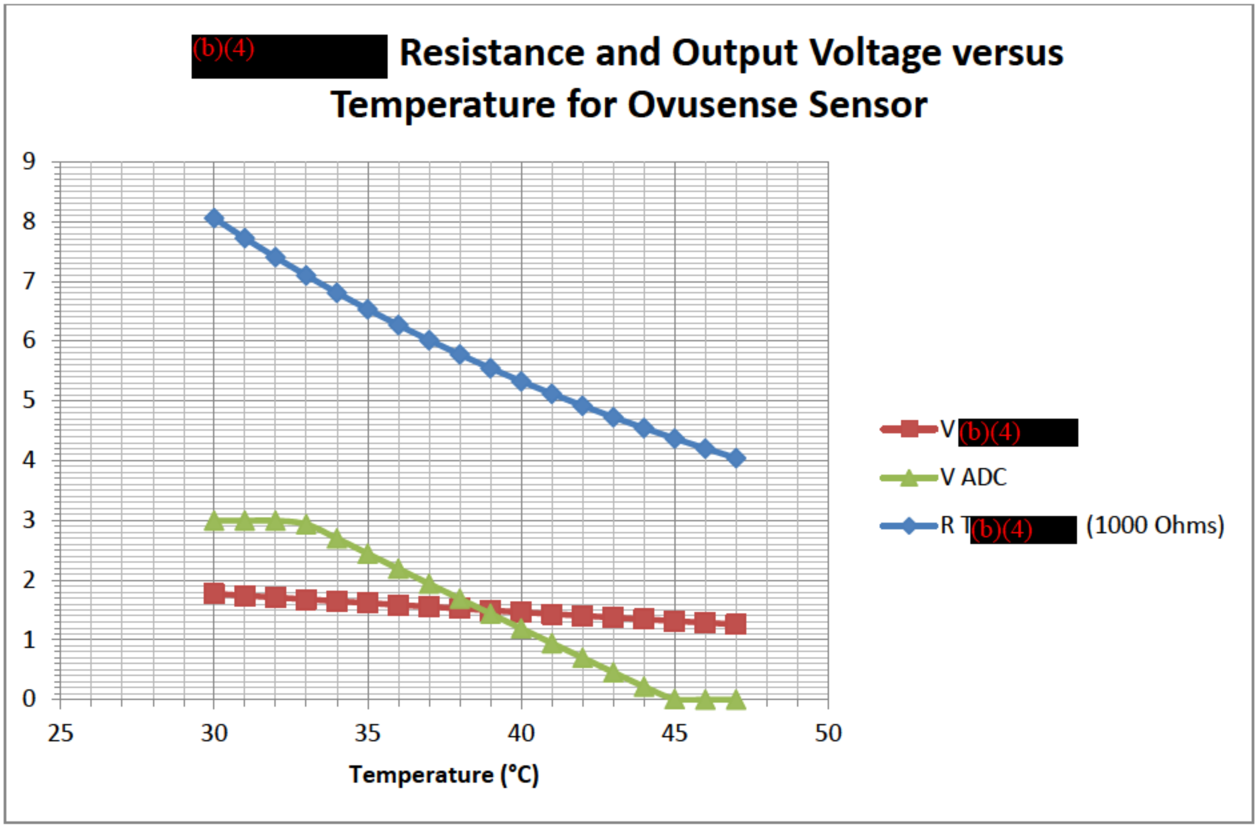
In order to analyse the (b)(4) circuit with prescaling amplifier it was simulated using SPICE using a generic op-amp model. The sensor is normally powered from a CR1632 Lithium button cell with a nominal Voltage of 3V. For the purposes of this analysis, the supply voltage is assumed to be a constant 3V.

Results

The results of the simulation are shown in the table and chart below:

V (b)(4) is the output of the potential divider containing the (b)(4) and provides the input to the amplifier. V ADC is the output of the amplifier and input to the ADC. The raw t(b)(4) resistance is also shown for reference.

Temperature °C	R (b)(4)	V (b)(4)	V ADC	ADC Count
30	8056	1.77	2.996	4090
31	7721	1.739	2.996	4090
32	7402	1.708	2.994	4087
33	7097	1.677	2.935	4006
34	6807	1.646	2.697	3681
35	6530	1.615	2.443	3335
36	6266	1.584	2.19	2989
37	6014	1.553	1.938	2645
38	5774	1.523	1.688	2304
39	5544	1.492	1.438	1963
40	5325	1.462	1.19	1624
41	5116	1.432	0.944	1289
42	4916	1.402	0.7	956
43	4724	1.373	0.456	622
44	4542	1.344	0.217	296
45	4367	1.314	0.0084	(b
46	4200	1.286	0.00058	1
47	4040	1.257	0.0004	1



The first thing to note is that the prescaling amplifier limits the operating temperature range of the sensor to approximately 33 to 44°C. Outside of this range the output of the operational amplifier and thus the input to the ADC reaches the supply rails. From this data it is also possible to calculate the gain of the amplifier.

Using the range 33-43°C, the change in input Voltage to the amplifier is 1.677 - 1.373 = 0.304V. For the same range, the change in amplifier output Voltage is 2.935 - 0.456 = 2.479V

Amplifier gain = ΔVout / ΔVin = 2.479 / 0.304 = 8.15 or 18.2dB

This is equivalent to approximately 3 extra bits of resolution in the ADC and reduces the LSB Voltage to a change of 89.9µV at the input of the amplifier.

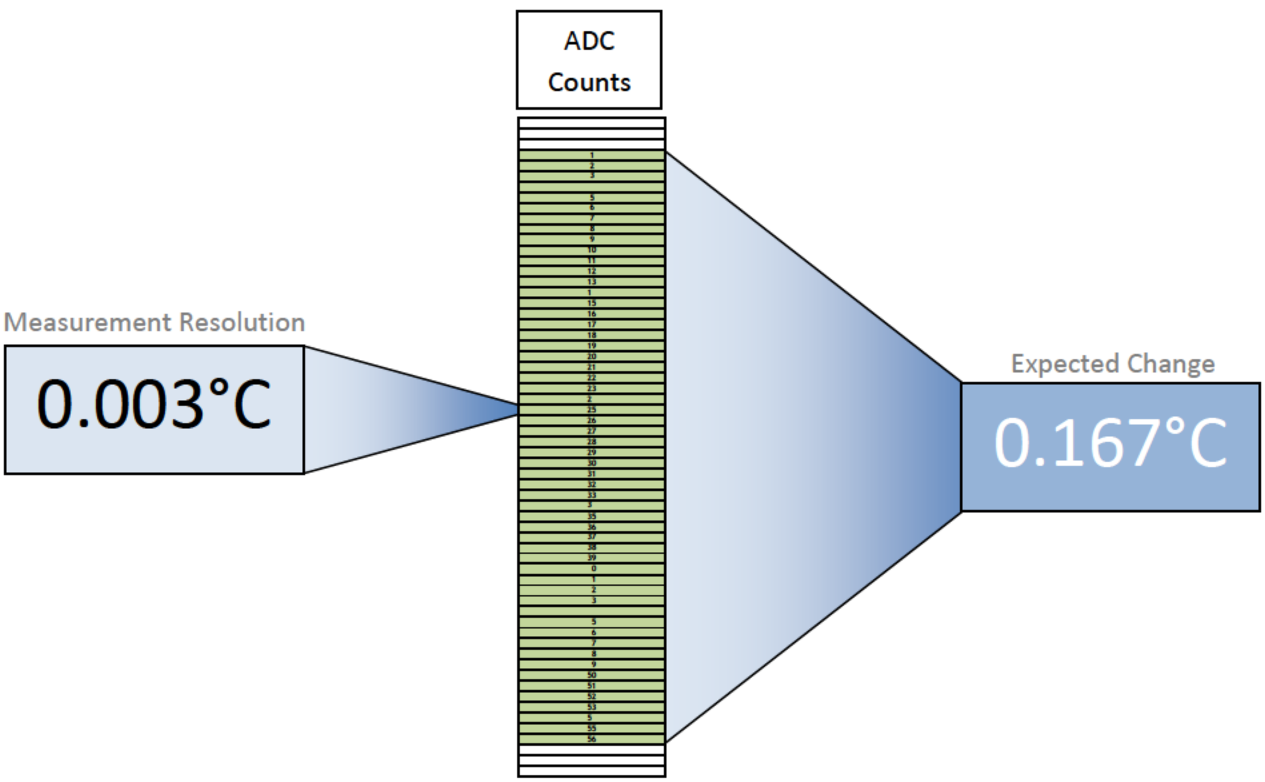
Rather than Voltages, what we actually need to know is the temperature resolution. Again, using the simulated data we can calculate the number of ADC counts per degree of temperature change. Between 33-43°C, the change in ADC count is 4006 - 622 = 3384. Dividing by 10 gives an average of 338 binary values per °C or 0.00296°C per ADC count. This is an average because there will be a slight non-linearity over the range due to the resistance-temperature curve of the [redacted]

Conclusion

The smallest temperature change which the sensor can detect is approximately **0.003°C.** Gain provided by the prescaling amplifier successfully targets the resolution of the ADC at the temperature range of interest and is usable between 33—44**°C.**

The temperature change of 0.167°C which the device is required to detect is equivalent to 56 ADC counts.

The function of the Sensor is to accurately convey a change in temperature, which it does by transmitting raw-data (ADC count) values to the Ovusense Reader. Any further translation of this data which may be performed by the Reader is therefore deemed unimportant to this study.



ATTACHMENT CRBR-2
LITERATURE REFERENCES

Application of a Method for Estimating Day of Ovulation Using Urinary Estrogen and Progesterone Metabolites

Donna Day Baird,[1] *D. Robert McConnaughey,*[2] *Clarice R. Weinberg,*[3] *Paul I. Musey,*[4] *Delwood C. Collins,*[5] *James S. Kesner,*[6] *Edwin A. Knecht,*[6] *and Allen J. Wilcox*[1]

Longitudinal epidemiologic studies of menstrual and reproductive function are more informative if one can identify day of ovulation. We previously developed a method for estimating day of ovulation that is feasible for epidemiologic studies. The method relies on the relative concentrations of estrogen and progesterone metabolites in daily first-morning urine specimens and does not require creatinine adjustment. This paper describes results of applying this method to a large study with 724 menstrual cycles from 217 women. The method estimated a credible day of ovulation in 88% of cycles. Missing data accounted for most of the failures. When we excluded anovulatory cycles (1%) and cycles with missing data, the method estimated a day of ovulation in 97% of cycles. Variance in luteal phase length was small for our sample, suggesting that this method of identifying a day of ovulation introduces no more measurement error than when day of ovulation is determined by plasma luteinizing hormone (LH), the standard clinical method. (Epidemiology 1995;6:547–550)

Keywords: epidemiologic methods, ovulation, urinary estrone-3-glucuronide, urinary pregnanediol-3-glucuronide, biomarkers.

[redacted]

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BASAL BODY TEMPERATURE: UNRELIABLE METHOD OF OVULATION DETECTION

[redacted]

TABLE 1. *Luteal Phase and Endocrine Parameters of Cycles during Which Basal Body Temperature Charts Were Obtained*

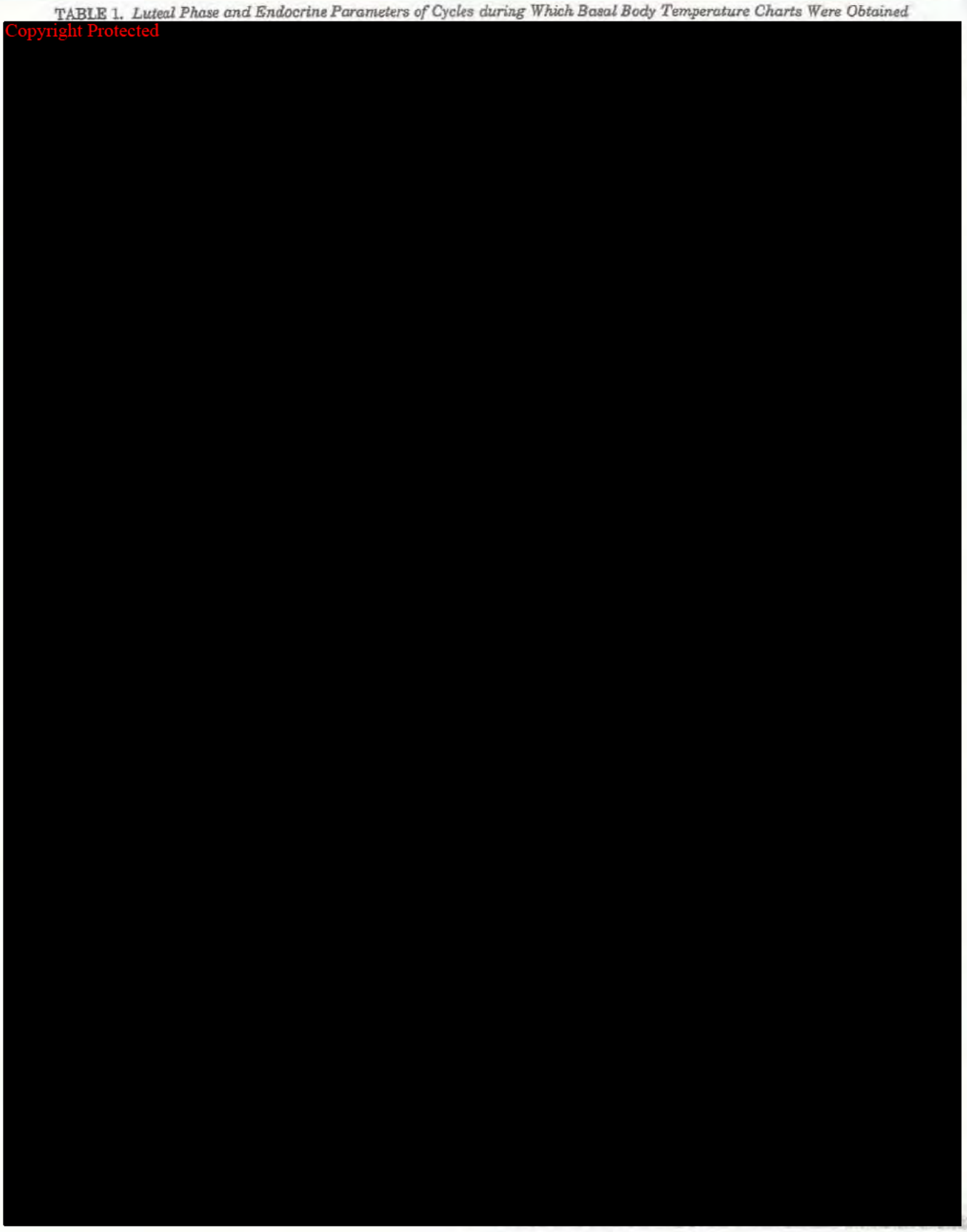
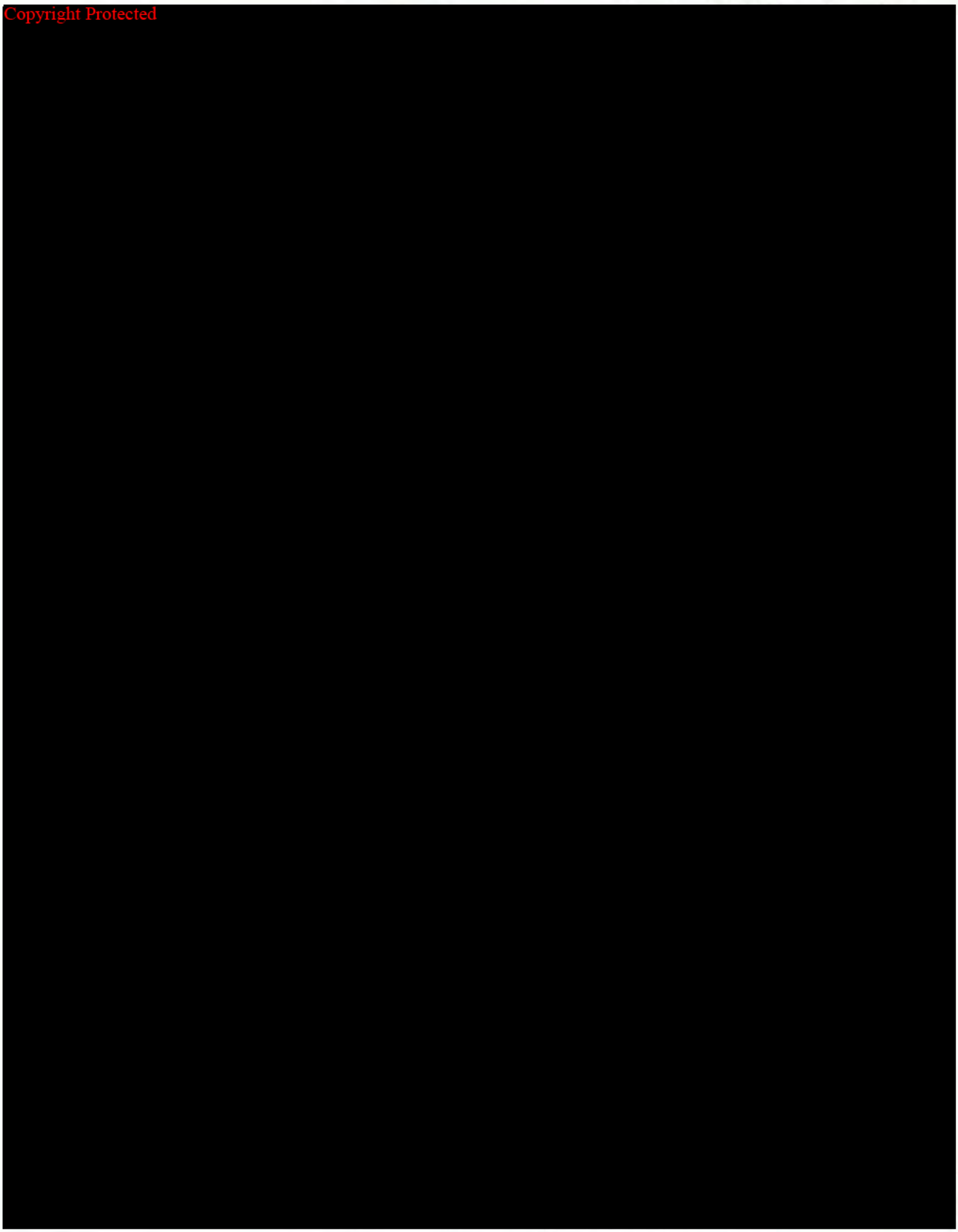


TABLE 2. *Evaluation of 77 Group I (Ovulatory) Basal Body Temperature Charts*

[redacted]



[redacted]

Daily Fecundability: First Results from a New Data Base

Bernardo Colombo[1]

Guido Masarotto[2]

on Behalf of the Menstrual Cycle Fecundability Study Group [Note 1]

Abstract

This multicentre study has produced a database of 7017 menstrual cycles contributed by 881 women. It provides improved knowledge on length and location of the "fertile window" (identified as of up to 12 days duration) and the pattern and level of daily conception probability. The day of ovulation was identified in each cycle from records of basal body temperature and mucus symptoms. By referencing days of intercourse to the surrogate ovulation markers, estimates of daily fecundability were computed either directly or by the Schwartz model, both for single and multiple acts of intercourse in the fertile window. The relationship between coital pattern and fecundability has been explored. Univariate analysis underlines the significant link with fecundability only of the woman's reproductive history.

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[2] Guido Masarotto (http://sirio.stat.unipd.it) is Professor of Statistics, University of Padua, Padua, Italy [Dipartimento di Scienze Statistiche, Via S.Francesco 33, 35121 Padova, Italy]

1. Introduction

In healthy non-contracepting sexually active couples fecundability, probability of conceiving a pregnancy during a menstrual cycle [Gini 1924, Gini 1928], depends on behaviour as well as physiology. Spermatozoa with the capability of fertilising the egg must already be present in the woman's reproductive tract at the time the egg is released at ovulation or must arrive there soon after. Number and timing of acts of intercourse in the cycle are an important factor. The width of the "fertile" window around ovulation, that is the number of days during which intercourse has a non-zero probability of resulting in conception, is uncertain. Widely diverging figures have been proposed in the literature, ranging from less than two to more than ten days [Glass and Grebenik 1954, Potter 1961, James 1963, Marshall 1967, Lachenbruch 1967, Glasser and Lachenbruch 1968, Barrett and Marshall 1969, Barrett 1971, Loevner 1976, Vollman 1977, Schwartz et al 1979, Trussell 1979, Schwartz, MacDonald, and Heuchel 1980, Royston 1982, Bongaarts and Potter 1983, World Health Organization 1983, World Health Organization 1985, Potter and Millman 1985, Bremme 1991, Weinberg, Gladen, and Wilcox 1994, Trussell 1996, Masarotto and Romualdi 1997, Weinberg et al 1998, Wilcox, Weinberg, and Baird 1998, Sinai, Jennings, and Arévalo 1999, Dunson et al 1999]. These estimates depend on data analysed, on conjectures accepted, on evaluations made with different approaches. Precise information on the pattern of daily fecundability and the width and location of the associated fertile interval in the menstrual cycle is of interest to both the biologist and the demographer. For the purpose of fertility regulation, the information is essential to those couples attempting to avoid pregnancy and those trying to achieve this end through appropriate timing of intercourse. The need for a large menstrual cycle data base, including a high number of conception cycles, for the purpose of clarifying various points of interest for basic knowledge and applications, has been repeatedly emphasised [Schwartz, MacDonald, and Heuchel 1980, James 1981, Potter and Millman 1986, Royston 1991, Royston and Ferreira 1999].

This paper introduces the results of an exercise performed in this direction with the co-operative collaboration of a group of organised centres giving advice to subjects interested in learning about the fertile phase of the woman and the use of a Natural Family Planning method to avoid or achieve pregnancies. To reach the planned target number of pregnancies (about 500) with a prospective design in a reasonable amount of time, the participation of several centres was necessary. In the following is given a summary description of the common protocol adopted and of the whole study design. We also describe the characteristics of the study subjects and centres and present preliminary analytical results. These results give special attention to covariates linked with the magnitude and pattern in the daily conception probabilities. They are compared with previous estimates from the literature. Mention is also made on ongoing lines of research opened by the available database.

2. Materials and Methods

2.1 Study Design and Population

The investigation was planned as a prospective cohort study conducted to determine the daily probability of conception among healthy subjects. The research protocol was reviewed and approved by the Institutional Review Boards of Fondazione Lanza (Padua, Italy) and Georgetown University (Washington D.C., U.S.A.). The study was co-ordinated from the Department of Statistical Sciences of the University of Padua (Padua, Italy).

From 1992 through 1996, 782 women were recruited with the collaboration of seven European centres (Milan, Verona, Lugano, Düsseldorf, Paris, London and Brussels) providing services on fertility awareness and natural family planning. The entry criteria for the subjects were: women experienced in use of a Natural Family Planning method; married or in a stable relationship; between 18th and 40th birthday at admission; having at least had one menses after cessation of breastfeeding or after delivery; not currently taking hormonal medication or drugs affecting fertility. Neither partner could be permanently infertile and both had to be free from any illness that might cause sub-fertility, e. g., endocrine disorders. It was also required that couples did not have the habit of mixing incidences of unprotected and protected intercourse. Women were excluded if any one of the previous criteria was not fulfilled.

Data from an additional 99 subjects were also included retrospectively in view of their relevance to the aims of the study. These data came from a prospective investigation carried out in Auckland, New Zealand, in 1979-85 into the relationship between the interval from intercourse to fertilisation and the sex of the baby conceived. In this study recruitment was made from couples of proven fertility who were contemplating a further pregnancy. For the purpose of timing intercourse, these couples were instructed on how to recognise the fertile period of the menstrual cycle and anticipate ovulation from changes in cervical mucus. The woman partner also recorded her basal body temperature each day. The study design restricted the couples to only one act of intercourse during the fertile phase of the cycle [France et al 1984, France et al 1992]. This requirement, not respected in a few instances, was the probable cause of subjects frequently dropping out of the study if they had not achieved a pregnancy after 3-4 cycles of trying. The resulting short observational period of sexually active non-conception cycles is a plausible source of positive bias in the estimate of the level of daily fecundability in the present study. Therefore, while the Auckland data is of significant value to other aspects of the study, only results from the seven European centres have been used in determining daily probabilities of conception.

A description of the centres, with the names of the local principal investigators, is given in [Note 1].

2.2 Data Collection

In each centre the local principal investigator instructed selected natural family planning teachers about the purpose and the requirements of the study. After completing the instruction phase, the teachers screened and selected the subjects for admission into the study. A woman satisfying all the inclusion criteria was enrolled only after having given written informed consent. In order to ensure complete subject anonymity and confidentiality, each subject was assigned a study number and only the teacher maintained a personal relationship with the subject. The mutual trust established in this relationship was essential to maintaining the collection of quality reliable data of a sensitive personal nature, which encompassed sexual behaviour.

All the charts were periodically sent to the Department of Statistics at the University of Padua, where uniform evaluation for all cases of the recorded basal body temperature (BBT), taken on awakening in the morning before engaging in any activity, was conducted. Coding of mucus typology, in accordance with agreed common rules, was done in the local centres.

2.3 Study Factors

At entry into the study, the following information was collected: the month and year of birth of the woman and of her partner; the number of previous pregnancies, if any; the date of her last delivery (or miscarriage) and of the end of breastfeeding, if relevant; the date of last oral contraceptive pill taken, if any. Subsequently, after the collection of data had begun, it was decided to add the date of marriage for married couples and the sex of any baby conceived and born during the period of the study. This latter information is available for a large proportion of subjects.

In each menstrual cycle the woman was asked to record on a chart the days of her period and of any disturbance such as illness, broken sleep. She was asked to also record her basal body temperature on the chart for as many days as necessary to determine a clear post-ovulatory rise. She was further asked to observe and chart her cervical mucus symptoms daily during the cycle, and to record every episode of coitus, with specification of whether it was unprotected or protected (barrier methods, withdrawal, …). Cycles in which even a single act of protected intercourse or of simple genital contact occurred were excluded from the analysis. The reliability of the information recorded of acts of intercourse was checked by the teacher in discussion with subjects at the end of each cycle. The importance of continuing to keep the record chart when subjects were trying to conceive a pregnancy was emphasised.

Charts were regularly collected by the teacher concerned. Following review at the local centre and scoring of the cervical mucus symptoms according to the common rules agreed for the study (Table 1), the charts were sent to the co-ordinating investigators in Padua for processing and entry into the data base [Note 2].

2.4 Definitions

A menstrual cycle was characteristically defined as the interval in days from the beginning of one period of vaginal bleeding until the commencement of the next, where day 1 was the first day of fresh red bleeding, excluding any preceding days with spotting.

The "three over six rule" was used to determine the BBT shift, defined as follows: the first time in the cycle that three temperatures were recorded all of which were above the level of the immediately preceding six daily temperature recordings. Such a rule has been shown to perform well in predicting the start of the infertile period following ovulation [Marshall 1968]. Exceptions to the rule were permitted: a) if there was one "spike" temperature among the six at the lower level (a spike temperature was defined as a temperature which was 0.2 centigrades or more above both its immediate neighbouring temperatures); b) or, in a cycle in which the impact of illness or other disturbances could be discounted, if there were at least six lower temperatures recorded before the upward shift. In analyses in which the BBT rise was used as a conventional indicator for timing ovulation, the last day of lower temperatures was designated as day 0, the "BBT reference day", to which all preceding and following days were scaled according to their distance by integer numbers.

The cervical mucus peak day was defined as the last day with best quality mucus, in a specific cycle of the woman, by sensation or appearance, known retrospectively. This peak day was taken as "Mucus reference day" and identified as day 0.

A conception was assumed in the presence of a pregnancy going on at 60 days from the onset of the last menses or when before that term a miscarriage was clinically detected.

2.5 Statistical Analysis

All the following statistical analyses, performed in the Department of Statistical Sciences, at the University of Padua, were limited to cycles in which ovulation occurred, or at least appeared to occur, and BBT reference day and/or mucus reference day was identified.

We first chose the window of potential fertility to be the series of days relative to the identified day of ovulation such that a cycle without intercourse during these days never resulted in a pregnancy. Daily estimates of probability of conception (a simple division: day by day, number of pregnancies/number of acts of intercourse) were then calculated using cycles with only one intercourse during the putative window. Since the act responsible for conception was unknown in cycles with more than one act of intercourse in the fertile interval, a more sophisticated procedure was needed to estimate globally the daily fecundability in the general case with one or more than one act of intercourse in the window. For this purpose the Schwartz model [Schwartz, MacDonald, and Heuchel 1980] (see [2.5.1]), which is an extension of the one suggested by Barrett and Marshall [Barrett and Marshall 1969], was used. For each cycle, the

probability of no conception is the probability the cycle is not viable plus the probability the cycle is viable and none of the intercourse acts result in successful fertilisation and survival to detection.

Inference was based on the likelihood: (i) parameter estimates were obtained by maximum likelihood, (ii) confidence intervals were then computed for each parameter of interest using the profile log-likelihood [Clayton and Hills 1993] and (iii) likelihood ratio tests were used to assess the significance of selected covariates.

Descriptive analysis was performed using SAS (see http://www.sas.com). R (http://www.r-project.org) was used to fit the Schwartz et al. model to the data. Functions and scripts are available upon request from the authors.

2.5.1 The Schwartz Model [Schwartz, MacDonald, and Heuchel 1980]

For each cycle, the observed outcome (conception/non conception) can be modelled as a Bernoulli random variable with parameter (the probability of success, i.e., the fecundability) that depends on the number and timing of the intercourse events.

Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] write fecundability as the product of three probabilities:

$$\text{fecundability} = P = P_0 \cdot P_f \cdot P_v$$

where $P_0 = \text{pr}(\text{that a fertilizable ovule is produced})$

$P_f = \text{pr}(\text{that the ovule is fertilized} \mid \text{fertilizable ovule})$

$P_v = \text{pr}(\text{that the conceptus stays alive for at least six weeks} \mid \text{fertilized ovule})$

To link P_f to the locations of the acts of intercourse, Schwartz et al. assume, following Barrett and Marshall [Barrett and Marshall 1969], that (i) different intercourse events have independent effects on the outcome and (ii) the probability of conception following intercourse only on day *i* (defined relative to the reference day [2.4]), $P_{f,i}$ say, is constant between couples and cycles.

Then, fecundability can be written as

$$P = k \cdot P_f = k \cdot \left[1 - \prod_i \left(1 - P_{f,i} \right)^{x_i} \right]$$

where *k*, called the cycle viability, denotes the product $P_0 \cdot P_v$, while

$$x_i = \begin{cases} 1 & \text{presence of intercourse in the i th day} \\ 0 & \text{otherwise} \end{cases} .$$

3. Results

3.1 Overview of the Sample

The characteristics of the 881 subjects enrolled in the various centres and of the 7017 considered cycles, with their outcomes, are summarised in Tables 2, 3, and 4. The number of subjects and contributed cycles varied markedly between centres and consequently, in order to obtain meaningful fecundability patterns from the analysis, some aggregation of data was made. In most analyses the data from Auckland were kept separate from those of the European centres owing to their specific features mentioned in [2.1] having an impact on the level of fecundability.

The average age of women in the study population was close to 29 years and was relatively similar at each centre (Table 2). The proportions of women of proven fertility and of those with past use of hormonal contraception are, however, very different among the centres. For the European centres overall, the percentage of women with at least one previous pregnancy was only 44.6% (range for centres: 30.8 - 73.1) while only 30.1% (range for centres: 11.4 - 56.2) had ever used hormonal contraception in the past (Table 2).

For these same centres, Table 3 underlines the high frequency of cases (96.4%) in which, when enough information was available, the described procedure allowed the BBT shift to be determined. However, when at least some information on temperature was recorded, in further 6.1% of the cycles the reference day could not be identified due to missing information on critical days, and in 1.6% due to disturbing illness. The proportion of cycles with determination – in similar conditions- of the mucus reference day is a little lower (94.1), owing to the particularly low percentage of the Paris subgroup. At that centre, in local usage, mucus symptoms are taken into consideration mainly for identification of the beginning of the “fertile” phase. The 575 detected pregnancies listed according to centres in Table 3 include both those continuing at 60 days from the onset of the last menses and the 49 clinically recognised miscarriages of the same period (also listed).

The figures of Table 4 -5591 cycles with BBT reference day (Table 4a) and 5928 with mucus reference day (Table 4b)- are linked with a conventional determination of the post-ovulatory phases starting after the respective reference days. They give an impression of a remarkable homogeneity between centres. The length of the phase after the peak mucus day in the various centres parallels similar results obtained in the WHO [World Health Organization 1983] study on the ovulation method. As expected, the length of the preovulatory phase shows a relative variability higher than that of the postovulatory one: e.g., for the European aggregate the coefficient of variation (4.74/16.7) is 25.7% in the first vs. 16.2% in the second.

It has to be noted that the two samples - with information on BBT and/or mucus - coincide in a sizeable proportion of cycles (5390 in the combined European group, 232 in Auckland: in the two sets of data both surrogate markers of ovulation were determined in about 80% of the cycles). On average, the peak mucus symptom occurred 0.31 days (S.d. 1.82) before the last low

temperature day in the European group (0.30 with S.d. 1.83 when the Auckland data were included).

The database can also be used in various forms to study the behaviour of the subjects. Table 5, showing the decline in the frequency of intercourse with the increasing age of each of the partners, provides an example. Three points have to be considered: the number of men above 40 is rather small; in conception cycles only acts of intercourse up to the 29th day of the cycle were counted; for obvious reasons, the data are for European centres only. The trend with age, evaluated through the arithmetic average (preferred to the median for sake of better evidence), and the higher coefficient of variation in non-conception cycles (61.3% vs. 49.7%), both support the reliability of the data collected. The small variations between the male and the female findings reflect differences in the number of subjects in the various classes and on the whole. For female partners, over all age groups, the median number of recorded acts of intercourse (10th, 90th percentiles) is equal to 6 days (3,11) in the conception cycles and to 4 (1,8) in the non-conception cycles.

Table 6 lists the distribution of 5390 cycles according to the interval in days between the two markers of ovulation (BBT reference day minus mucus reference day). We know already - from [3.1] - the value of the average distance between those days. There is some translation between the two reference terms, which -though small - can influence the comparative distributions of cycles, and of intercourse episodes and pregnancies allocated to the various days of the respective fecundability window. In the majority (62.4%) of the cycles the two markers are within ± one day and the difference is greater than ± two days in 17% of the cycles. This suggests that estimates of day-specific pregnancy probabilities should not depend greatly on which marker is used for ovulation. However, we cannot rule out possible overestimation of the fertile interval relative to BBT or mucus reference day compared with the width of the fertile interval relative to the true day of ovulation. Although efforts were made to rule out errors in documentation of BBT or cervical mucus, measurement errors can result due to unavoidable biological variability. In future work, such measurement errors could be assessed and corrected using recently developed statistical methodology [Dunson and Weinberg 2000, Dunson et al in press].

3.2 Fertility Windows: Direct Estimates of Fecundability

In order to find windows of fertility - around the BBT or the mucus reference day - to be used for estimates of daily fecundability, an exploratory analysis was made, changing width and location of chosen windows. For each reference marker, it was found that, when no intercourse episodes were ascertained in a 12-day window, no pregnancy was recorded. Eight among the 12 days preceded the day 0 and three came afterwards.

Then, direct estimates of daily fecundability were computed inside these windows. In this initial determination, only cycles with a single act of intercourse in a window were selected. The ratio of instances in which the acts of one day resulted in conception to the total number of acts of intercourse of the same day gave, for that day, an estimate of the probability of conception. The results are presented in Table 7 for the combined European centres (top section) and with inclusion of Auckland for all centres (bottom section). The differences in the number of cycles between the bottom and the top grouping give the contribution from Auckland. The two sets of probabilities are very different, particularly when the impact of the Auckland data, in terms of number of conception cycles, is relevant: direct estimates obtained for this site are on the average about double those of the European ones. It is worth mentioning that no one of the almost 350 intercourse episodes of the third day of the high BBT gave rise to a conception. And also that Auckland conforms to the other centres concerning the width of the window, which might be shorter, even when due account is taken of the smaller sample size.

A similar exercise was performed, with data only from European centres, with the aim of obtaining more precise fecundability estimates by increasing the number of contributing cycles through use of a smaller window, in which the probability of having single intercourse episodes is increased. Cycles, however, were eliminated from consideration in which, while only a single act of intercourse occurred in the shorter window, conception might have been due (though certainly with a small probability) not to that coital act but to intercourse episodes falling outside the window. From this point of view, were considered relevant, for cycles having intercourse on day -6, the three days -9, -8, -7, reduced to two (-8, -7) for cycles with intercourse on day -5, and to one (-7) in cycles with intercourse on day -4. Similarly, were excluded from the analysis cycles with intercourse on day +2. The elaboration was extended to evaluate a parallel window around the mucus reference day. The results for both analyses are shown in Table 8. In absolute terms, the main differences between the two sets of probability are observed on days -3 and 0. Considering - besides random errors and the small shift in BBT versus mucus - that the two aggregates of cycles are different, the estimates of fecundability, daily and total, appear in good agreement. Worthy of attention is the finding that the peak mucus day is not the one with maximum fecundability. In each aggregate, the four days preceding the reference day are the most relevant for cycle fecundability.

3.3 Estimates through a Model

In the presence of multiple acts of intercourse during the fertile interval of a cycle, the probability of conception due to a single act on any day cannot be estimated directly. One has to make use of a model whose computed coefficients may lead to an evaluation of daily fecundability. For this purpose, in the following, estimates of day by day conception probabilities are obtained through the application of the Schwartz model [Schwartz, MacDonald,

and Heuchel 1980], summarised in [2.5.1]. This model has been repeatedly used in the literature, and by that it allows comparisons with other experiences.

The model estimates of daily fecundability for the European subjects are presented in Table 9, with confidence intervals obtained through the profile maximum likelihood [Clayton and Hills 1993], at the 90% level. The chosen windows are those already seen. The two sets of data have a different composition, but once again they underline in both cases the significance of higher rates in the four days preceding the respective reference day.

In Figure 1, the daily estimates relative to each of the two markers of ovulation are presented. These estimates are based on the 5390 cycles from the European centres for which both reference days are available. There is a total of only 386 pregnancies, since for 48 there is information only on the peak mucus day, for 49 only on BBT shift, and nothing in 4 instances. The given confidence intervals are at the 90% level. Several points may be mentioned: a) in the two sets of estimates, though the total number of cycles is the same, the number of those with at least one intercourse episode in the window differs: 2917 for BBT and 2843 for mucus, respectively. This difference will have an effect, though small, on the respective areas under the curve; b) one has to remember the mentioned average distance between the two reference days and its possible effects (see para 7 of [3.1]); c) the estimates based on the mucus symptom conform less well to a bell shaped pattern as observed with the BBT window; d) the dip at day -3 found through the mucus symptom repeats what seen in the data set of Table 9 and also in the direct estimates of Table 8: a point deserving further elaboration.

It appears that the BBT reference day may be a slightly better (i.e. less error prone) marker of ovulation day, since the estimates, compared with those around the mucus reference day, are higher on the days of peak fertility (i.e. days -3 to -1) and lower on the days towards the edge of the window.

In Table 10 the results for the 12 days BBT window are compared with fecundability estimates reported from five other similar studies. A few notes will clarify the limits of these comparisons. The discrepancies between the different sets of probabilities can be attributed - apart from random errors- to different characteristics of the subjects, to distinct procedures followed in determining the ovulation reference day and to the inclusion or exclusion of early miscarriage in the counted pregnancies. The probabilities reported by Schwartz et al. [Schwartz et al 1979] are direct estimates from single donor artificial inseminations per cycle by donors. The data by Weinberg et al. [Weinberg et al 1998] and by Wilcox et al. [Wilcox, Weinberg, and Baird 1998] come from recruitment from the general population of subjects wanting to achieve a pregnancy. In the other two studies, the information was collected in centres providing services on fertility awareness and natural fertility regulation. Weinberg et al [Weinberg et al 1998] were able to include through assay of hCG very early pregnancies losses, otherwise undetected by clinical diagnoses. In the same set of pregnancies, Wilcox et al. [Wilcox, Weinberg, and Baird 1998] considered only those clinically diagnosed, that is events more similar to those considered in the present aggregate of European centres. In the other studies there were no important

differences in the recording of pregnancies. In conception cycles with multiple acts of intercourse in the "fertile" window, Bremme [Bremme 1991] chose to assign pregnancy to the intercourse which occurred closest in time prior to or coinciding with the presumed day of “ovulation”: a procedure leading to a bias which increased fecundability rates as the “ovulation” day was approached. For the probabilities computed in Weinberg et al [Weinberg et al 1998] and in Wilcox et al. [Wilcox, Weinberg, and Baird 1998] ovulation day (i.e. day 0) was identified using the decline in the ratio of oestrogen to progesterone metabolites in the urine that accompanies luteinization of the ovarian follicle [Baird et al 1991]. This steroid based marker should be less error-prone than markers on BBT or mucus, but should not deviate systematically from the last day of low temperature used in the other studies, as in the present data base. Apart from Bremme and Schwartz et al [Schwartz et al 1979], the other four sets of estimates were based on the Schwartz model [2.5.1].

Figure 2 shows a graphical comparison of the pattern of conception probabilities in the BBT window for four subgroups (centres or combinations of centres) and for the whole European experience. The results for the Auckland subjects clearly differ from those of the other instances. The other three subgroups consisted of the Verona centre, Milan aggregated with Lugano because of similarity of NFP teaching content and method, and the four remaining European centres combined because of their small sample sizes. The homogeneity of the fecundability data between the three European subsets is striking. The maximum likelihood ratio test of significance of the differences between the three European subsets gives $p>0.10$. The merging of their records in a unique European group appears reasonable: this will form the basis of all subsequent analyses on the level of fecundability

Figures 3, 4 and 5 focus on the link between three covariates pertaining to the female subjects and fecundability in the window around the BBT reference day. The covariates evaluated are: the reproductive history of the woman, by comparing subjects with and without a previous pregnancy (Figure 3); the woman's age, by dividing the subjects into three age groups, 18-24 yrs (103 subjects), 25-34 yrs (596), and 35-39yrs (83; Figure 4); and past use or non use of oral contraception (Figure 5). The difference in the level of fecundability of the women of proven fertility versus the unproven group is very significant ($p = 0.014$). In the group with unproven fertility, though the subjects obviously believed they were fertile, their number would include some with undiagnosed infertility or sub-fertility as in the general population. Furthermore, at least in one Italian centre, subjects may have been included in the study who were seeking help in achieving a pregnancy after a prolonged experience of failure. No marked differences in fecundability rates were observed in the three age groups ($p>0.10$), though the sample sizes in the younger and older groups are relatively small. When the subjects were divided into those below and those above the median age (29 years), again no significant difference in fecundability was found between the two groups ($p>0.10$, data not shown). Similarly, no significant differences ($p>0.10$) are seen in the daily fecundability when comparisons are made between past use or no previous use of oral contraception. It should be

noted, however, that the number of women having used this method of contraception in the three cycles preceding their entry into the study is extremely low (3.0%).

Two further results pertaining to the cycles are presented in Figures 6 and 7. Figure 6 is based on the data of Table 6. The whole set of cycles is divided into three groups according to the time difference between the BBT reference day and the peak mucus day: group 1, negative difference (1569 cycles, 29.1% of the total); group 2, difference equal to 0 and 1 days (2553, 47.4%); group 3, greater than 1 day (1268, 23.5%). For each of the three derived sub-sets the Figure shows the pattern of estimated daily conception probabilities. Attention is drawn to the sub-set in which the two reference points (almost) coincide, and therefore should support each other as giving a rather good approximate indication on the time of ovulation. The pattern of conception probabilities appears very concentrated, falling after a continuous rise extending over five days, with a maximum at day –2, approaching zero at both extremes (see also Wilcox et al. [Wilcox, Weinberg, and Baird 1998]). The pattern is somewhat similar in group 3, though more elevated at beginning of the ascending part and then falling abruptly on day zero, remaining then at this level. When the peak mucus day occurs after the BBT reference day (group 1) the probability pattern is very irregular with two maxima (on day -3 and day 0). The difference between the three sets of probabilities is very significant (p=0.020).

Figure 7 illustrates the pattern of daily fecundability for two different subsets of cycles, one with the window around the BBT shift (3175 cycles with at least one intercourse in the window, 434 pregnancies) and the other with the window around the mucus reference day (3265 cycles, 435 pregnancies). The two subsets are each further divided according to the length of the conventional follicular phase of the cycles, <16 days and > = 16 days The very different shape of the two derived patterns of fecundability is highly significant (p=0.003 for BBT, p<0.001 for mucus). The differences in probability levels on, say, day –4 depending on the said length is very strong. Evidently the distance -4 does not have the same meaning for all cycles: as does the distance at day zero, though with inverse relationship in the probabilities of the two subsets. The evidence is the same for both BBT and mucus which tends to exclude systematic errors in the identification of the reference days as an explanation. There is a biological foundation for such a result or does this serve as a hint to consider more stable the positioning of ovulation in the cycle and more variable that of the conventional surrogate indicators?

4. Discussion

The startling variety of suggestions concerning the width of the "fertile window" found in the literature depends in part from conceptual approaches adopted. To try and measure the window summing lifetime of sperm and ovum -less the time needed for capacitation of spermatozoa -is a deductive theoretical solution. But when, instead of a single cycle, a mixture of cycles of a group of women is considered, due account has to be taken of the biological variability of both patterns and its interaction. When trying to make evaluations starting from aggregates of distinct empirical experiences, one should be sure that the single cases record real facts uniformly and homogeneously, without the impact of confounding factors. According to Potter and Millmann [Potter and Millman 1985], the lines of research followed to clarify the point can be grouped into two categories. In the first one, assumptions are made on mean fecundability and average coital pattern: a chosen model allows us to estimate the length of the fertile period assuring compatibility between the two. In the second, starting from estimated daily probabilities, given a certain coital pattern, the fecundability in a cycle is derived.

The procedure followed in this exercise falls into this second class. That is, it starts from and deals with aggregations of distinct ascertained facts. One aspect of the documentation that has been collected needs to be stressed here: that is, its reliability about type and timing of what is essential for the study of fecundability, the acts of intercourse. This has been assured by the long experience of the co-operating centres, an agreed rigorous protocol, the follow up of the ongoing work through periodical meetings of the Principal Investigators, the scrupulous screening of the forms arriving at the co-ordinating centre.

At the same time, the main weakness of the information has to be underlined: the reliance on the surrogate indicators of the true day of ovulation, the BBT shift and the peak mucus day. The distribution of deviations between these markers and the true ovulation day is poorly known (see, e.g. [Hilgers, Abraham, and Cavanagh 1978, Hilgers and Bailey 1980, France 1982, Guida et al 1999]). Several recent studies have obtained estimates of error in BBT reference day. There have been small validation studies and Dunson et al. [Dunson et al 1999] present estimates. These studies suggest that most cycles have errors of less than ± one day. A major challenge is to try to obtain correct measures of daily fecundability, possibly using the methods of Dunson and Weinberg [Dunson and Weinberg 2000] and Dunson et al. [Dunson et al in press]. Furthermore, while ovulation is practically instantaneous, we have only information on the level of days.

The Schwartz et al. [Schwartz, MacDonald, and Heuchel 1980] model (see [2.5.1]) chosen has its merits: it rests on appealing biological hypotheses, and in general fits well the data. But it has weaknesses: it is based on rather simplistic assumptions; with high frequency of intercourse it tends to underestimate observed fecundability; the parameter k, supposed to measure the so-called cycle viability, is not independent from the pattern of intercourse episodes. But it is not the place, here, to enter into a thorough discussion of comparative evaluation of advantages and

disadvantages of different proposed or conceivable models, or of other approaches to the desired estimation.

These words of caution do not detract significance for applications from the main results of the study in the area of fertility regulation. Couples attempting pregnancy should maximise their intercourse frequency during the four days preceding the first upward shift of the basal body temperature or the peak mucus day. In both distinct sets of cycles the maximum level of conception probabilities is achieved in the second day before the reference point: 0.255 in the window around BBT reference day and 0.203 in the other case. Couples wanting to avoid pregnancy are informed that the unsafe period might be extended up to 11-12 days. The computed confidence intervals may help to qualify the situation obtaining at the two extremes of the window, where the probabilities of conception are very low. In both sets, eight days before the reference point the estimated probability is 0.003, which means, approximately, a pregnancy every 26 years: but the computed upper confidence limits reach 0.011. Obviously, these conclusions are drawn from *a posteriori* observation, but concerning the determination of the beginning of the pre-menstrual infertile phase they provide sufficient information. For other purposes, needing day to day decisions, apart from some observations currently possible - as a first evidence of the mucus symptom -, it would be advantageous to be able to make reliable forecasts. For this sake, an improvement of usual calendar methods through a sequential procedure using updated accumulated observations made on preceding cycles might prove useful.

The results obtained are of interest also from a demographic point of view. Contraception has an obvious impact as a confounding factor on the link between so-called natural and actual fertility of a population. The said results make clear how behaviour together with physiology has an influence on natural fertility. What matters is not only frequency of coitions, but also their allocation to the different days of the fertile interval. The maximum daily fecundability estimated in the BBT window is .255 (Table 9) which corresponds to an average number of 3.92 cycles needed for obtaining a pregnancy, while after one year (roughly 13 cycles) 2.2% subjects remain without success. Couples with at least three acts of intercourse in the same window –roughly representing those attempting a pregnancy- reach a proportion of .227 conception cycles on the whole. This corresponds to 4.41 cycles for a pregnancy and 3.5% of failures in a year.

After the elaboration for the whole data set, some covariates are taken into consideration, one by one: centres, reproductive history and age of the women, and previous use of oral contraception. Homogeneity was observed among three sets of European populations both in pattern and level of conception probabilities and in the extension of the fertile window. Auckland shows the same pattern but a significantly higher level of probabilities. Similar results are reached in the other elaboration on the European set, with a clear difference in the level of daily fecundability only according to previous reproductive experience. Attention should be drawn, however, on the upper age limit of 40 years for the women, the lack of standardisation with respect to the reproductive history of the woman and the decline of *k* with increasing age. The

interrelations between covariates -for instance between age and reproductive history of the women- show that for the distinct evaluation of the impact of various factors, a multivariate analysis approach is needed. A consideration of heterogeneity between units due to unobservable phenomena has to be added to this. The study design is rather complex, hierarchical and multilevel. Considering the women subjects, there are days in a cycle, cycles in a woman, women in a centre, various centres. At each level there is involvement of specific covariates and there is unobservable heterogeneity between the units. Furthermore, there is a confounding factor, the age of the partner.

If one wants - particularly in view of more efficient applications in the field of fertility regulation - to try to make clusterization of subjects, the results by cycle shown in Figures 6 and 7 suggest that longitudinal analyses of consecutive cycles within women are needed to characterise them. Also, longitudinal analysis of cycles might prove useful in clarifying the impact of physiology and behaviour on the outcomes: a rather intriguing area of study since at every step the event -number and allocation of acts of intercourse- may change.

These examples show that the database presented in this paper offers possibilities of investigation along several lines of research.

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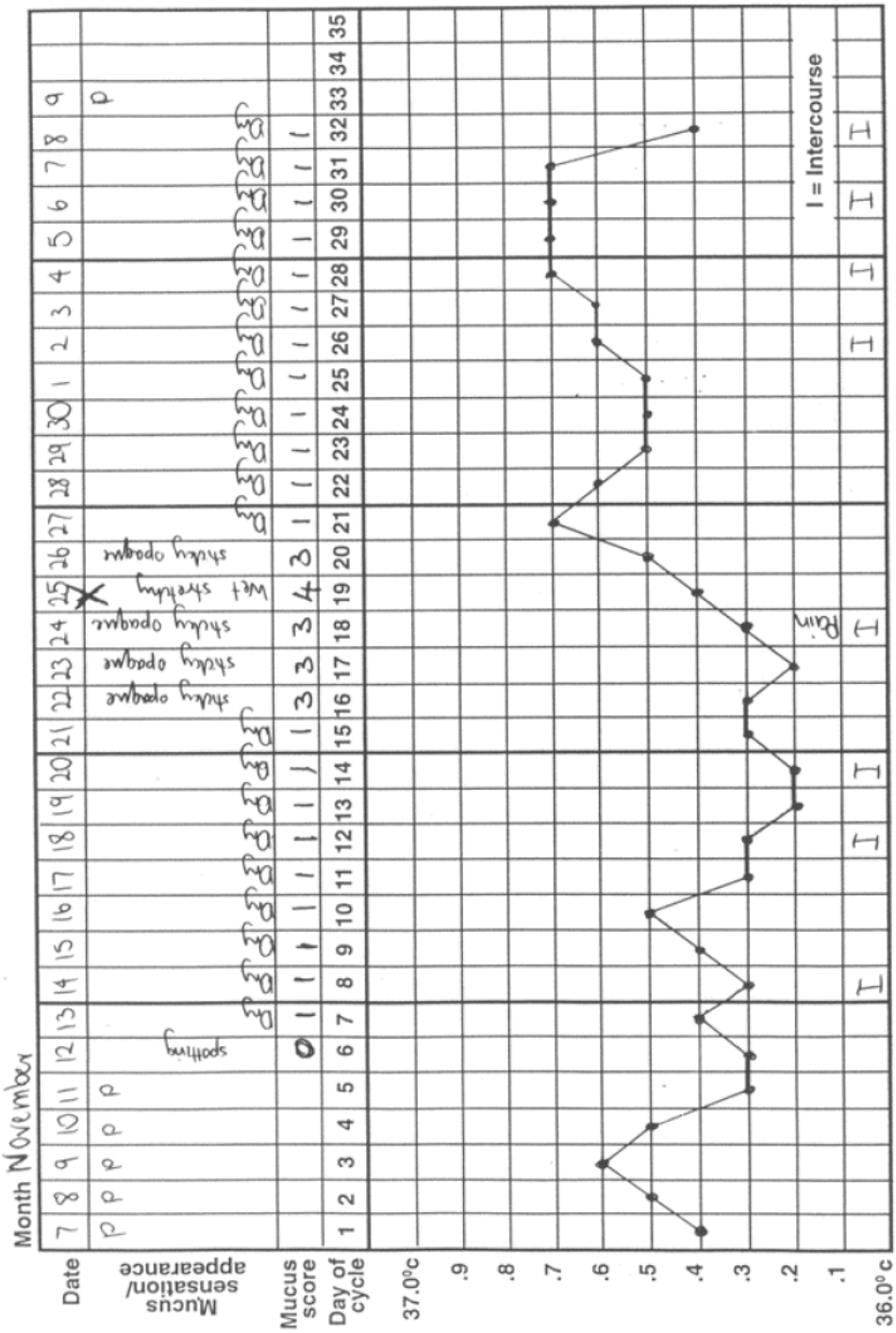
Notes

1. The Study Group Investigators were: Michele Barbato, M.D., Centro Ambrosiano Metodi Naturali, Milan, Italy, Priscilla Coppieters, M.D., Fédération Francophone pour le Planning Familial Naturel, Couple-Amour-Fécondité, Brussels, Belgium, John France, PhD., DSc., Research Center in Reproductive Medicine, Department of Obstetrics and Gynaecology, University of Auckland School of Medicine, Auckland, New Zealand, Sandro Girotto, M.D., Istituto per l'Educazione alla Sessualità e alla Fertilità (INER – Verona), Verona, Italy, Christian Gnoth, M.D., Natürliche Familien Planung, Frauenklinik, University of Düsseldorf, Germany, Jane Knight, R.N., Fertility UK, London, United Kingdom, Lucia Rovelli, Centro Metodi Naturali di Lugano, Lugano, Switzerland, Cathérine Renard Denis, Centre de Liaison des Equipes de Recherche, Paris, France, and General Coordinators: Bernardo Colombo, Emer. Prof., and Guido Masarotto, Prof., Dipartimento di Scienze Statistiche, Università degli Studi, Padua, Italy.
2. An example of a menstrual cycle record chart received in the coordinating centre of Padua. The cross on the date indicates the peak mucus day.

Subject code : 12.010.0142 001



References

Baird DD, Weinberg CR, Wilcox AJ, McConnaughy DR. Using the ratio of urinary oestrogen and progesterone metabolites to estimate day of ovulation. *Statistics in Medic.*, 1991, 10, 2: 255-266.

Barrett JC. Fecundability and coital frequency. *Popul. Studies*, 1971, 25, 2: 309-313.

Barrett JC, Marshall J. The risk of Conception on Different Days of the Menstrual Cycle, *Popul. Studies*, 1969, 23, 3: 455-461.

Bremme J. Sexualverhalten und Konzeptionswahrscheinlïchkeit (Auswertung einer prospektiven Studie zur Natürlichen Familienplanung), *Thesis***,** 1991, Med. Fakultät der Heinrich. – Heine – Universität, Düsseldorf

Bongaarts J, Potter LG. Fertility, Biology and Behavior, 1983, New York, Academic Press, 35-38.

Clayton D, Hills M. Statistical Models in Epidemiology, 1993, Oxford, Oxford University Press: 124-128.

Dunson DB, Baird DD, Wilcox AJ, Weinberg CR, Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation, *Human Reproduction*, 1999, 14, 7 : 1835-1839.

Dunson DB, Weinberg CR. Modeling Human Fertility in the Presence of Measurement Error, *Biometrics*, 2000, 56, 1: 288-292.

Dunson DB, Weinberg CR, Baird DD, Kesner JS, Wilcox AJ. Assessing human fertility using several markers of ovulation, *Statistics in Medic.*, in press.

France JT. The Detection of Ovulation for Fertility and Infertility. *Recent Advances in Obstetrics and Gynaecology.* Ed J Bonnar, 1982, No 14: 215-239.

France J, Graham FM, Gosling L, Hair P. A prospective study of the preselection of sex of offspring by timing intercourse relative to ovulation. *Fertility and Sterility*, 1984, 41, 6: 894-900.

France J, Graham FM, Gosling L, Hair P, Knox BS. Characteristics of natural conceptual cycles occurring in a prospective study of sex preselection: Fertility awareness symptoms, normal levels, sperm survival, and pregnancy outcome. *Intern. J. of Fert.*, 1992, 37, 4: 244-255.

Gini C. Prime ricerche sulla “fecondabilità” della donna, *Atti reale Istituto Veneto di Scienze Lettere ed Arti*, 1924, 83, 2: 315-344.

Gini C. Premières recherches sur la fécondabilité de la femme, *Proc. of the Intern. Mathem. Congress, Toronto, Aug. 11-16, 1924, Vol. II*, Fields JC Ed., 1928, Toronto, The Univ. of Toronto Press: 889-892.

Glass D., Grebenik E. *The Trend and Pattern of Fertility in Great Britain*, Papers of the Royal Commission on Population, 1954, 6, 1: 255.

Glasser JH, Lachenbruch PA. Observations on the Relationship beetween Frequency and Timing of Intercourse and the Probability of Conception, *Popul. Studies*, 1968, 22, 3: 399-407.

Guida M, Tommaselli GA, Palomba S, Pellicano M, Moccia G, Di Carlo C, Nappi C, Efficacy of methods for determining ovulation in a natural family planning program, *Fertility and Sterility*, 1999, 72, 5: 900-904.

Hilgers TW, Abraham GE, Cavanagh D. Natural family planning. I. The peak symptom and estimated time of ovulation, *Obstetrics and Gynecology,* 1978, 52, 5: 575-582.

Hilgers TW, Bailey AJ, Natural family planning. II. Basal body temperature and estimated time of ovulation, *Obstetrics and Gynecology,* 1980, 55, 3: 333-339

James WH. Estimates of Fecundability, *Popul. Studies,* 1963, 17, 1: 57-65.

James WH. Distributions of Coital Rates and of Fecundability, *Social Biology*, 1981, 28, 3-4: 334-341.

Lachenbruch PA. Frequency and Timing of Intercourse: Its Relation to the Probability of Conception, *Popul. Studies*, 1967, 21, 1: 23-31.

Loevner DR. Estimation of Risks of Conception and the Fertile Period, *B. A. Thesis*, 1976, Princeton University.

Marshall J. Analyse statistique du moment de la concéptìon en rélation avec l'élévation de la température sur 5013 cycles, *Actes du Congrés Mondial la Population*, Belgrade, 30 Août – 10 Septembre. 1965. *Vol. II: Fécondité, Planification de la famille, Mortalité*, 1967, New York, Nations Unies: 305-307.

Marshall J. A field trial of the basal body-temperature method of regulating births. *The Lancet*. 1968, 2: 810.

Masarotto G, Romualdi C. Probability of conception on different days of the menstrual cycle: an ongoing exercise, *Advanc. in Contrac.*, 1997, 13, 2-3: 105-115.

Miolo L, Colombo B, Marshall J, A data base for biometric research on changes in basal body temperature in the menstrual cycle, *Statistica,* 1993, 53, 4: 563-572.

Potter RG. Length of the fertile period, *Milbank Memor. Fund Quart*. 1961, 39, 1: 132-162.

Potter RG, Millman SR. Fecundability and Frequency of Marital Intercourse: A Critique of Nine Models, *Popul Studies*, 1985, 39, 3: 461-470.

Potter RG, Millman SR. Fecundability and Frequency of Marital Intercourse: New Models Incorporating the Aging of Gametes, *Popul. Studies*, 1986, 40, 1: 159-170.

Royston JP. Basal body Temperature, Ovulation and the Risk of Conception, with special Reference to the Lifetimes of Sperm and Egg, *Biometrics,* 1982, 38, 2: 397-406.

Royston P. Identifying the Fertile Phase of the Human Menstrual Cycle, *Statistics in Medic.*, 1991, 10, 2: 221-240.

Royston P, Ferreira A. A New Approach to Modelling Daily Probability of Conception, *Biometrics,* 1999, 55, 4: 1005-1013.

Schwartz D, Mayaux MJ, Martin-Boyce A, Czyglik F, David G. Donor insemination: conception rate according to cycle day in a series of 821 cycles with a single insemination, *Fertil. Steril.*, 1979, 31, 2: 226-229.

Schwartz D, MacDonald PDM, Heuchel V. Fecundability, coital frequency and the viability of ova, *Popul. Studies,* 1980, 34, 2: 397-400.

Sinai I, Jennings V, Arévalo M. The Two Day Algorithm: A New Algorithm to Identify the Fertile Time of the Menstrual Cycle, *Contraception*, 1999, 60, 2: 65-70.

Tietze C. Probability of conception resulting from a single unprotected coitus, *Fertil. Steril.,* 1960, 11, 5: 485-488.

Trussell J. Natural fertility: measurement and use in fertility models, in *Natural Fertility* (Léridon H, Menken J Eds.), 1979, Liège, Ordina Editions: 31-64.

Trussell J. Conception Probabilities by Cycle Day, *Memorandum,* 1996, Office of Population Research, Princeton University.

Vincent B. Atlas de Courbes Thermiques, 1964, Edition 4, Nantes, Centre de Documentation et d'Information Conjugale : 60.

Vollman RF. Assessment of the fertile and sterile phases of the menstrual cycle *Intern. Rev. of Nat. Fam. Plann.,* 1977, 1, 1: 40-47.

Weinberg CR, Gladen BC, Wilcox AJ. Models Relating the Timing of Intercourse to the Probability of Conception and the Sex of the Baby. *Biometric*s, 1994, 50, 2: 358-367.

Weinberg CR, Wilcox AJ, Baird DD, Gladen BB. The probability of conception as related to the timing of intercourse around ovulation. *Genus,* 1998, 54, 3-4: 129-142.

Wilcox AJ, Weinberg CR, Baird DD, Post-ovulatory ageing of the human oocyte and embryo failure, *Human Reproduction*, 1998, 13, 2: 394-397.

Wood JW. Dynamics of Human Reproduction – Biology, Biometry, Demography, 1994, New York, Aldine de Gruyter: 143-150, 295-305.

World Health Organization. A prospective multicentre trial of the ovulation method of natural family planning. III. Characteristics of the menstrual cycle and of the fertile phase, *Fertil. Steril.,* 1983, 40, 6: 773-778.

World Health Organization. A prospective multicentre study to develop universal immunochemical tests for predicting the fertile period in women, *Intern. J. Fert.,* 1985, 30, 3: 18-30.

Table 1:
Classification and codification of mucus symptoms.*

Code of mucus type	Feeling	Appearance of mucus
0	No information	No information
1	Dry, rough and itchy feeling or nothing felt	Nothing seen, no mucus
2	Damp feeling	Nothing seen, no mucus
3	Damp feeling	Mucus is thick, creamy, whitish, yellowish, not stretchy/elastic, sticky
4	Wet, slippery, smooth feeling	Mucus is transparent, like raw egg white, stretchy/elastic, liquid, watery, reddish (with some blood)

* If there are different mucus observations on one day, the most fertile characteristic of the mucus observed determines the classification.

Table 2:
Characteristics of women and men participating in the exercise.

Centres	No. of women	Age of women Mean (Sd)	Age of men Mean (Sd)	No. of women with at least one past pregnancy (% of women)	No. of women with past use of hormonal contra-ception (% of women)
Verona	214	28.6 (3.54)	30.7 (4.16)	66 (30.8)	63 (29.4)
Milan	272	28.7 (3.56)	31.3 (4.73)	109 (40.1)	31 (11.4)
Lugano	13	29.3 (4.50)	32.1 (3.99)	5 (38.5)	4 (30.8)
Paris	104	29.3 (4.52)	31.4 (5.42)	76 (73.1)	38 (36.5)
Düsseldorf	105	28.2 (4.48)	30.4 (4.86)	44 (41.9)	59 (56.2)
London	45	31.6 (4.68)	34.0 (4.60)	29 (64.4)	24 (53.3)
Brussels	29	29.7 (4.52)	31.6 (3.78)	20 (69.0)	16 (55.2)
Total European	782	28.9 (4.00)	31.2 (4.70)	349 (44.6)	235 (30.1)
Auckland	99	29.9 (3.13)	32.3 (3.87)	96 (97.0)	34 (34.3)

Table 3:
Characteristics of cycles and their outcomes

Centres	No. of cycles	No. of cycles with identification of BBT reference day (% of cycles*)		Mucus reference day (% of cycles†)		No. of cycles with at least one coition in the window‡	No. of detected pregnancies (% of cycles)		No. of miscarriages (% of pregnancies)	
Verona	1279	1133	(97.9)	1246	(98.3)	827	171	(13.4)	11	(6.4)
Milan	3288	2840	(95.4)	3051	(95.8)	1351	151	(4.6)	20	(13.2)
Lugano	57	56	(98.2)	57	(100)	48	13	(22.8)	0	(0)
Paris	787	680	(95.8)	576	(74.0)	340	63	(8.0)	5	(7.9)
Düsseldorf	654	615	(97.8)	650	(99.4)	257	41	(6.3)	3	(7.3)
London	320	250	(95.8)	272	(96.1)	181	30	(9.4)	5	(16.7)
Brussels	339	286	(99.0)	314	(95.2)	171	18	(5.3)	3	(16.7)
Total European	6724	5860	(96.4)	6166	(94.1)	3175	487	(7.2)	47	(9.7)
Auckland	293	238	(94.8)	285	(97.3)	215	88	(30.0)	2	(2.3)

* The percentage is the proportion of cycles with the identified rise in the BBT over the cycles with enough information on the BBT
† The percentage is the proportion of cycles with the identified peak of the mucus over the cycles with enough information on the mucus
‡ Window around the last day of hypothermia

Table 4:
Characteristics of non conception cycles with identification of reference days.

a) With BBT reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	982	29.0	(5.04)	16.4	(5.01)	12.6	(2.09)
Milan	2711	29.1	(3.89)	16.7	(3.93)	12.4	(2.09)
Lugano	44	27.2	(2.24)	14.7	(2.73)	12.5	(2.19)
Paris	620	29.3	(4.92)	17.1	(4.91)	12.2	(1.08)
Düsseldorf	574	28.3	(3.73)	16.3	(3.68)	12.0	(1.89)
London	224	29.8	(4.68)	17.2	(4.56)	12.5	(2.46)
Brussels	271	28.7	(3.63)	16.3	(3.74)	12.4	(1.94)
Total European	5426	29.0	(4.26)	16.6	(4.26)	12.4	(2.07)
Auckland	165	29.5	(4.37)	16.7	(4.64)	12.8	(2.36)

b) With mucus reference day*

Centres	No. of cycles	Total length of cycles		Duration of phases			
				Preovulatory		Postovulatory	
		Mean	(S.d.)	Mean	(S.d.)	Mean	(S.d.)
Verona	1084	29.1	5.04	15.6	4.91	13.4	2.22
Milan	2913	29.1	3.95	16.6	3.93	12.5	2.07
Lugano	44	27.2	2.24	14.2	2.48	13.0	2.19
Paris	534	29.2	5.01	16.9	5.12	12.3	2.04
Düsseldorf	610	28.3	3.69	15.9	3.52	12.4	2.01
London	245	29.3	4.29	17.4	4.04	11.9	2.54
Brussels	301	28.6	3.56	15.2	3.68	13.4	2.07
Total European	5731	29.0	4.25	16.3	4.23	12.7	2.16
Auckland	197	29.0	4.16	16.2	4.21	12.8	2.43

* Conventionally: Preovulatory phase = until the last day of hypothermia or, respectively, the peak mucus day, included; Postovulatory phase = the remaining part of the cycle.

Table 5:
Average number of acts of intercourse per cycle (European centres)

Age classes (years)	Intercourse of women in				Intercourse of men* in			
	Conception cycles†		Non conception cycles		Conception cycles†		Non conception cycles	
	Mean	(S.d.)	Mean	(S.d..)	Mean	(S.d.)	Mean	(S.d.)
18-24	7.1	(3.19)	5.2	(3.10)	7.4	(3.86)	5.7	(3.47)
25-29	6.5	(3.08)	4.9	(2.82)	6.6	(3.17)	5.1	(3.08)
30-34	5.5	(3.03)	4.2	(2.73)	6.0	(3.00)	4.3	(2.54)
35-39	5.1	(2.30)	3.7.	(1.96)	5.3	(2.65)	4.0	(2.52)
≥40					5.6	(2.62)	4.2	(2.19)
Total	6.2	(3.08)	4.5	(2.76)				

* There are 34 cycles in which the man's age is missing
† In conception cycles, only the first 29 days since the onset of the menses are taken into consideration.

Table 6:
Distribution of cycles according to the distance between the reference days in 5390 cases in which both days have been identified (European centres).*

Distance in days	Number of Cycles	Percent	Number of pregnancies
-9	1	0.0	0
-8	1	0.0	0
-7	1	0.0	0
-6	10	0.2	0
-5	16	0.3	1
-4	108	2.0	5
-3	203	3.8	15
-2	420	7.8	26
-1	809	15.0	56
0	1434	26.6	97
1	1119	20.8	80
2	692	12.8	58
3	356	6.6	29
4	170	3.2	13
5	33	0.6	4
6	14	0.3	2
7	1	0.0	0
8	1	0.0	0
9	0	0.0	0
10	1	0.0	0
Total	5390	100	386

* The distance is the difference: day of last low BBT minus mucus reference day.

Table 7:
Direct estimation of fecundability in the window [-8,3] around the BBT reference day for the European centres and all the centres.

		Distribution of single acts of intercourse in the window												
	Cycles	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	Total
European centres	Conc. cycles	1	1	4	2	9	8	4	5	2	0	4	0	40
	All cycles	265	151	92	55	40	29	26	25	29	35	85	343	1175
	Ratio	0.004	0.007	0.043	0.036	0.225	0.276	0.154	0.200	0.069	0	0.047	0	0.034
All centres	Conc. cycles	1	1	6	5	13	10	12	13	9	2	5	0	77
	All cycles	269	154	97	67	47	35	37	40	46	54	94	348	1288
	Ratio	0.004	0.006	0.062	0.075	0.277	0.286	0.324	0.325	0.196	0.037	0.053	0	0.060

Table 8:
Direct "adjusted" estimation of fecundability in the window [-6,1] around the reference day (European centres).

Reference		Distribution of single acts of intercourse in the window								
		-6	-5	-4	-3	-2	-1	0	1	Total
	Conc. cycles	3	2	11	12	10	10	4	2	54
BBT	All cycles	90	59	50	45	41	54	59	60	458
	Ratio	0.033	0.034	0.220	0.267	0.244	0.185	0.068	0.033	0.118
	Conc. cycles	4	4	11	8	10	13	6	6	62
Mucus	All cycles	86	71	59	43	42	50	52	80	483
	Ratio	0.047	0.056	0.186	0.186	0.238	0.260	0.115	0.075	0.128

Table 9:
Daily estimates in cycles with one or more acts of intercourse in the windows
(European centres; Schwartz et al. model [see 2.5.1])

	BBT reference day		Mucus reference day	
Intercourse day vs reference day	Probability of conception	Lower-Upper 90% Confidence Interval L U	Probability of conception	Lower-Upper 90% Confidence Interval L U
-8	0.003	0.000 - 0.011	0.003	0.000 - 0.011
-7	0.014	0.003 - 0.035	0.000	0.000 - 0.004
-6	0.027	0.013 - 0.049	0.045	0.026 - 0.071
-5	0.068	0.037 - 0.108	0.078	0.046 - 0.118
-4	0.176	0.124 - 0.236	0.181	0.131 - 0.238
-3	0.237	0.179 - 0.277	0.114	0.068 - 0.173
-2	0.255	0.193 - 0.277	0.203	0.145 - 0.270
-1	0.212	0.157 - 0.272	0.177	0.126 - 0.237
0	0.103	0.059 - 0.155	0.135	0.089 - 0.192
1	0.008	0.000 - 0.046	0.067	0.035 - 0.109
2	0.035	0.016 - 0.060	0.020	0.005 - 0.049
3	0.000	0.000 - 0.003	0.005	0.000 - 0.015
No. of cycles	3175		3265	
No. of pregnancies	434		435	
k	0.277		0.301	

Table 10:
Comparison of estimates of daily probability of conception

Intercourse day vs. reference day	Schwartz et al [1979]	Schwartz, MacDonald, and Heuchel [1980]	Bremme, [Bremme 1991]	Weinberg et al [1998]	Wilcox, Weinberg, and Baird [1998]	European centres
-8						0.003
-7			<0.005			0.014
-6			0.018			0.027
-5		0.04	0.076	0.100	0.04	0.068
-4	0.08	0.14	0.100	0.155	0.13	0.176
-3	0.20	0.20	0.152	0.139	0.08	0.237
-2	0.13	0.20	0.235	0.274	0.29	0.255
-1	0.21	0.34	0.270	0.312	0.27	0.212
0	0.15	0.14	0.331	0.331	0.08	0.103
1	0.11	0.07	0.065			0.008
2	0.09					0.035
No. of conception cycles	631*	103†	109	192‡	144§	434§§

* After at least 21 days of hypothermia. The “zero” point is the last day of hypothermia, following [Vincent 1964].

† Pregnancies of at least six weeks duration in a given cycle.

‡ Of which 48 (25%) early losses within six weeks and 15 clinical spontaneous abortions after six weeks from the onset of the last menses

§ The same set of data as in ‡, but excluding the 48 early losses (i.e. within 6 weeks of LMP). The probabilities used to generate the figure in [Wilcox, Weinberg, and Baird 1998] were kindly provided by Dr. David Dunson.

§§ Ongoing at 60 days from the onset of the last menses, included clinically diagnosed abortions in this period (window around BBT reference day).

Figure 1:
Daily fecundability in cycles with both BBT and mucus reference day (day 0), with 90% confidence intervals. European centres.

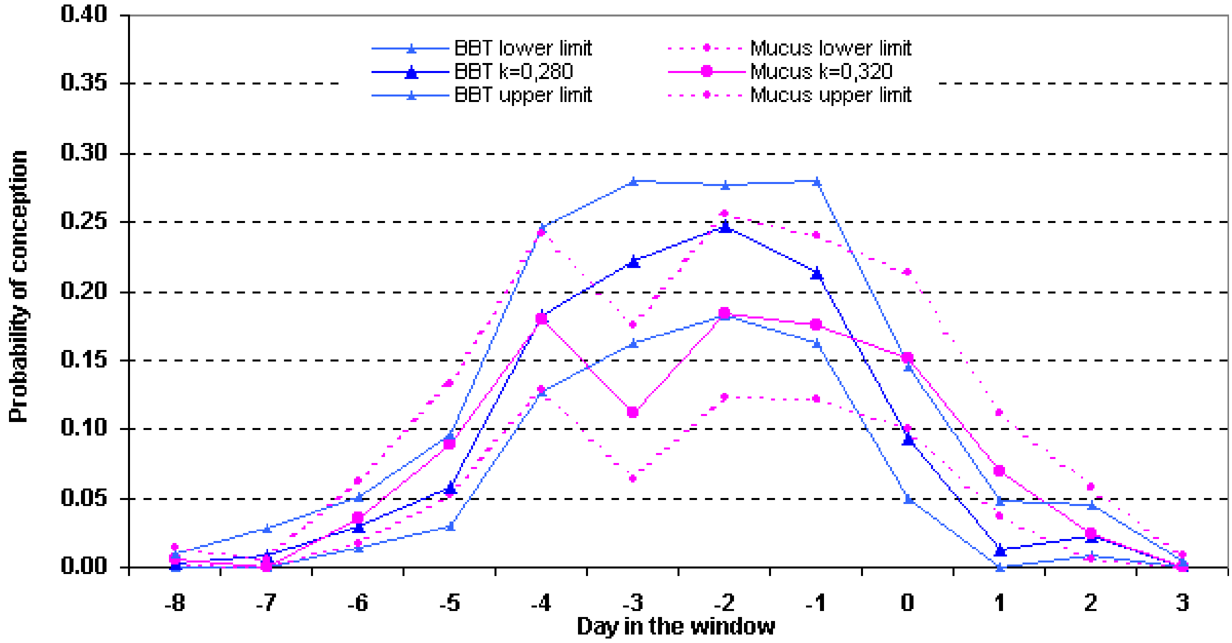


Figure 2:
Daily fecundability around the BBT reference day. Various subgroups.

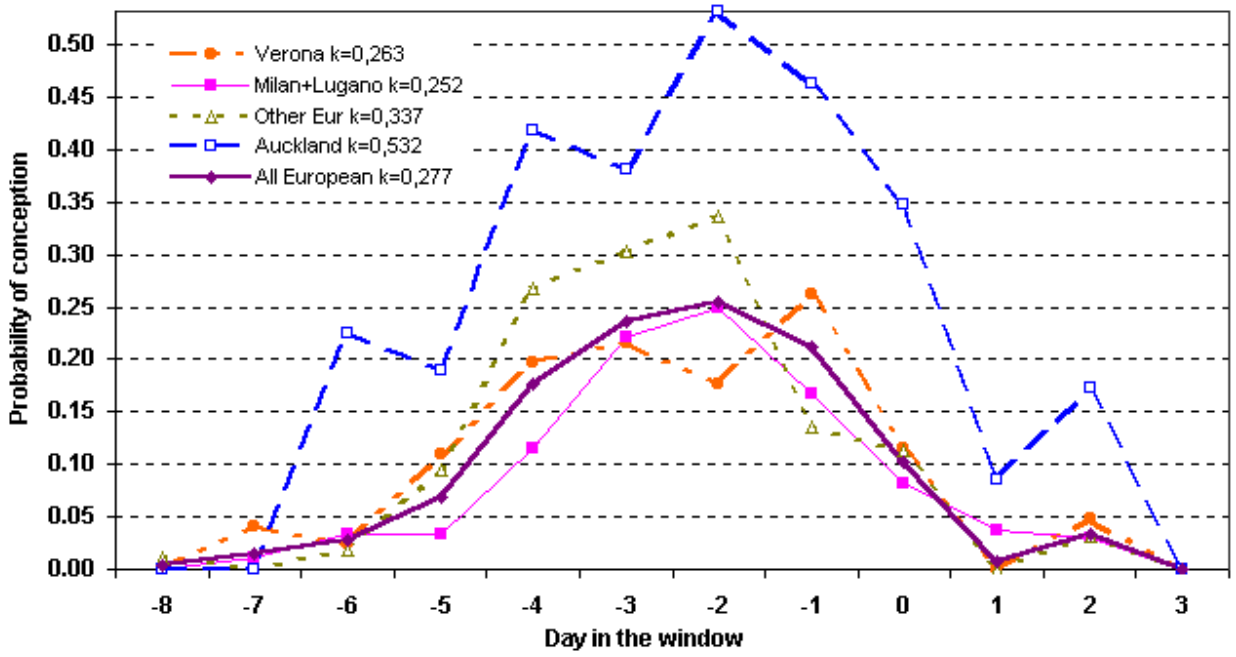


Figure 3:
Daily fecundability around the BBT reference day for women with or without previous pregnancies. European centres.

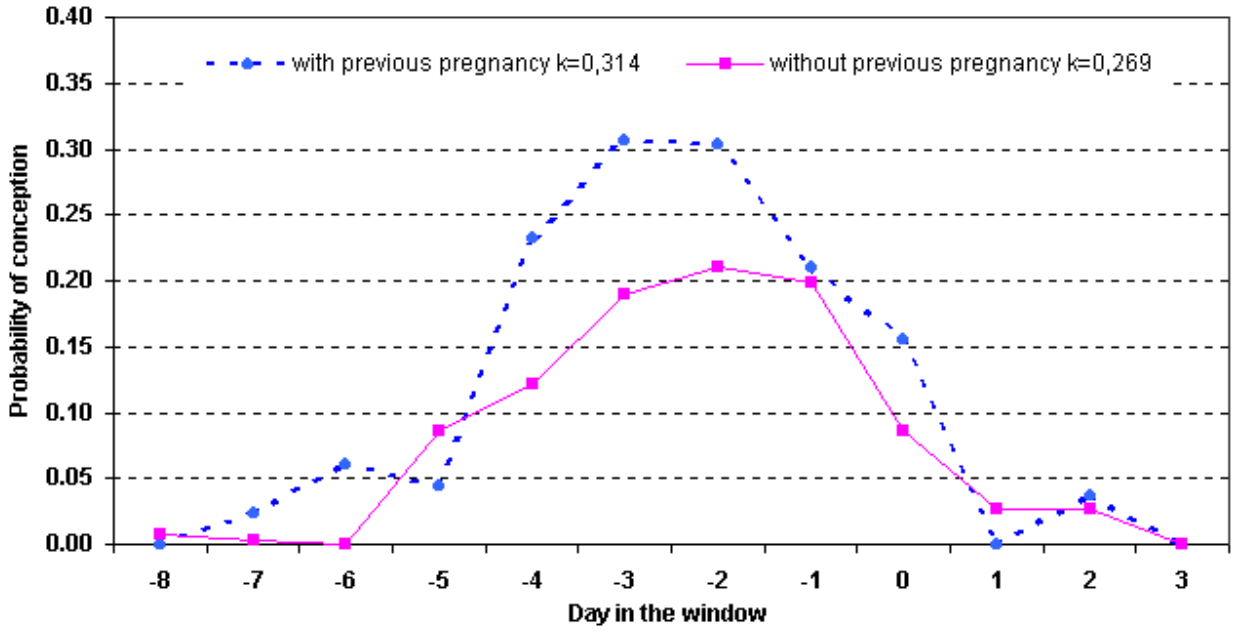


Figure 4:
Daily fecundability around BBT reference day by age classes (18-24 years, 25-34, 35-39) of women. European centres.

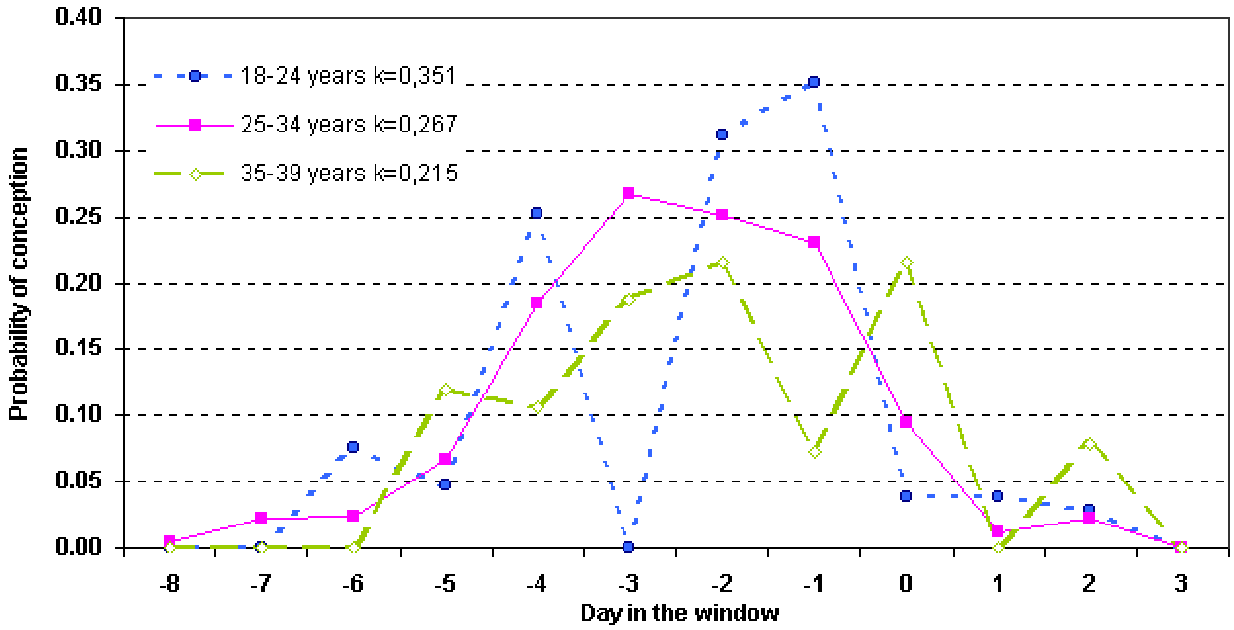


Figure 5:
Daily fecundability around BBT reference day according to the past use or no use of oral contraception. European centres.

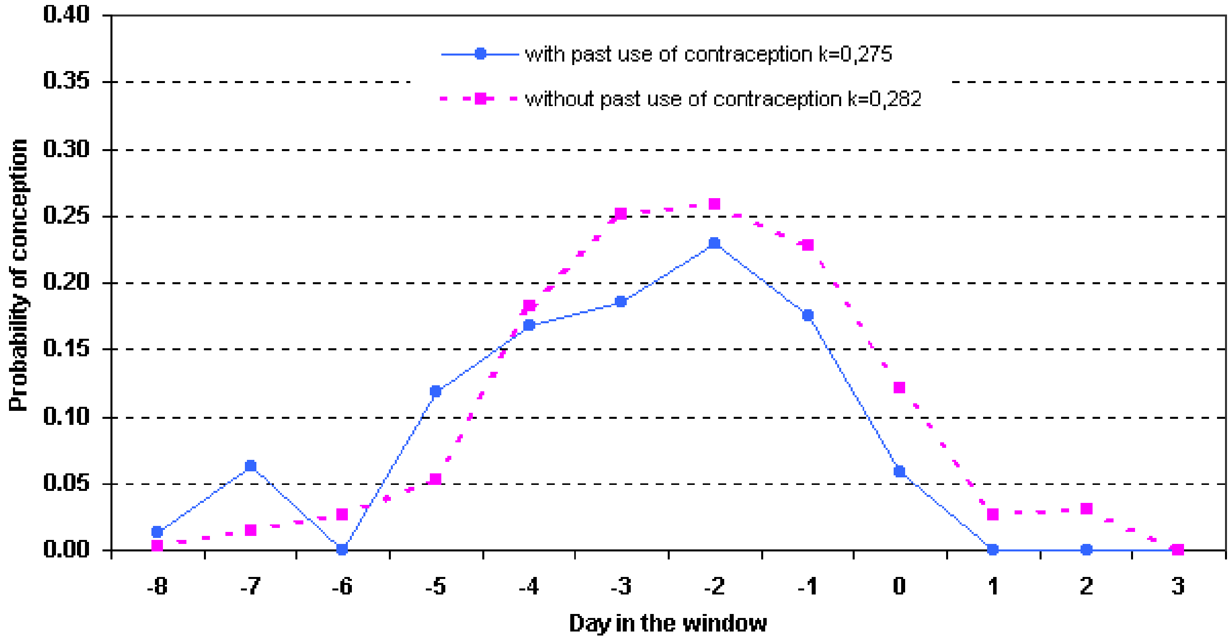


Figure 6:
Daily fecundability around BBT reference day according to the distance "BBT minus mucus reference day" (distance equal to 0 or 1 days, higher than 1 day, negative). European centres.

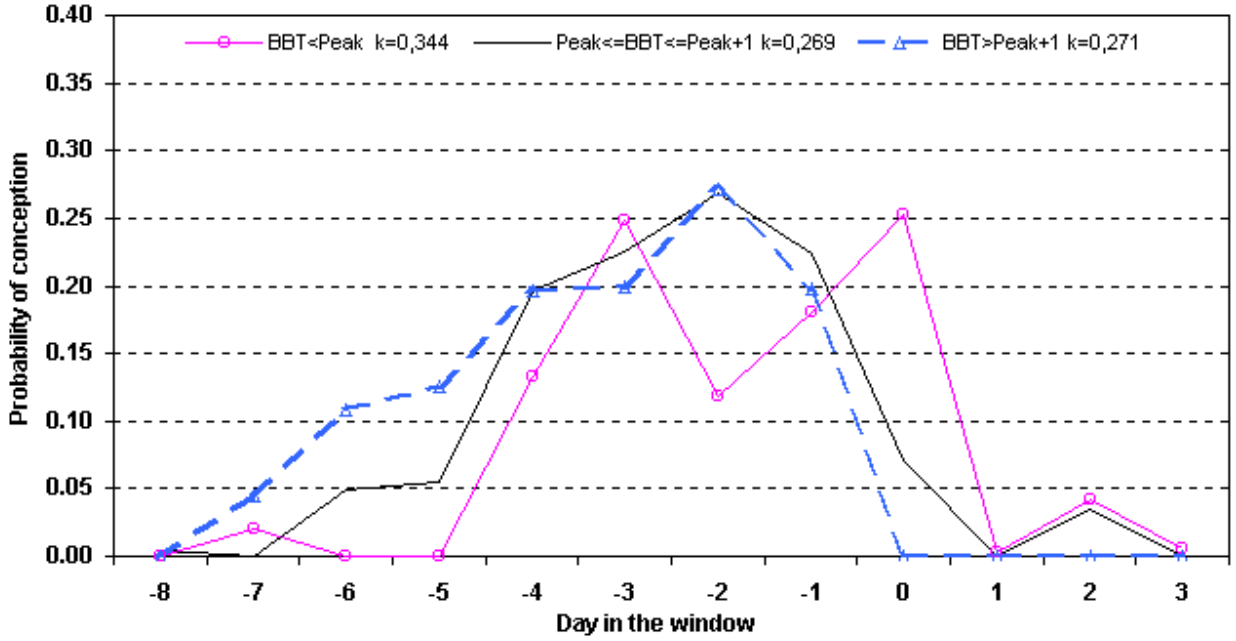
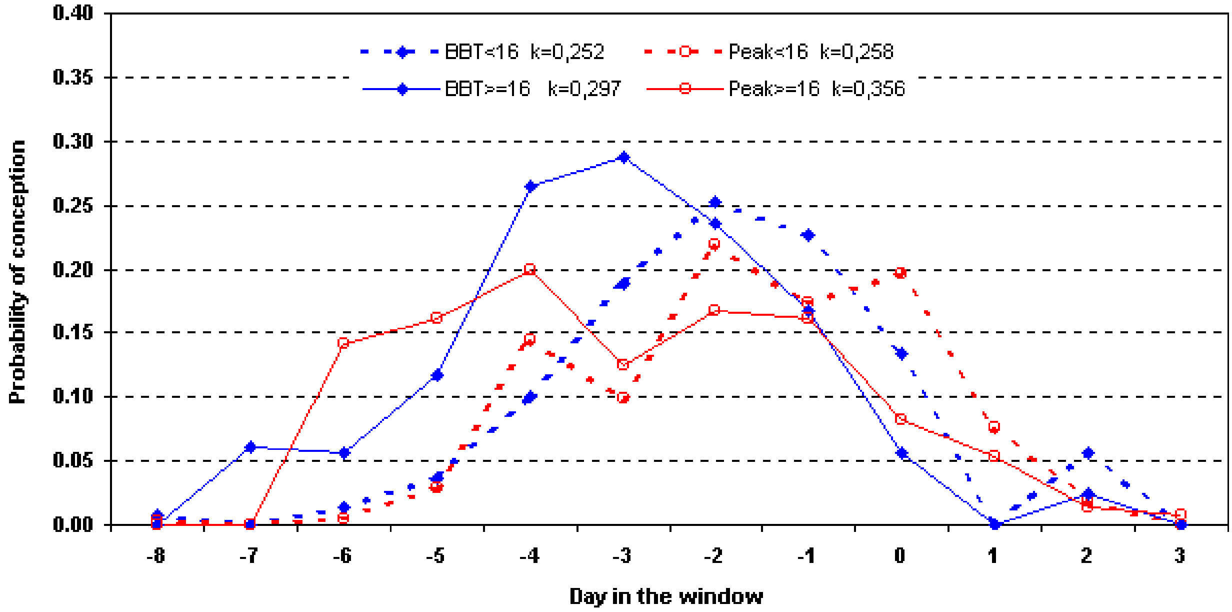


Figure 7:
Daily fecundability around BBT or mucus reference days according to the length of the respective conventional preovulatory phase (<16 days, ≥16 days). European centres.



Am J Physiol Regulatory Integrative Comp Physiol
279: R1316–R1320, 2000.

Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring

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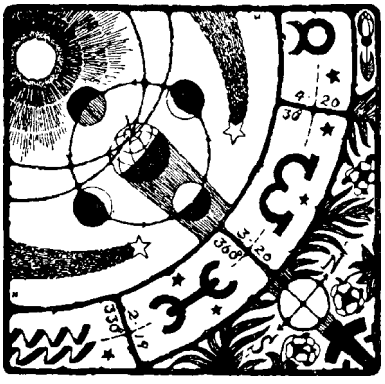

Human Reproduction vol.14 no.7 pp.1835–1839, 1999

Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation

Gynecological Endocrinology, June 2005; 20(6): 305 – 312

FERTILITY

Determination of the fertile window: Reproductive competence of women – European cycle databases

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Abstract

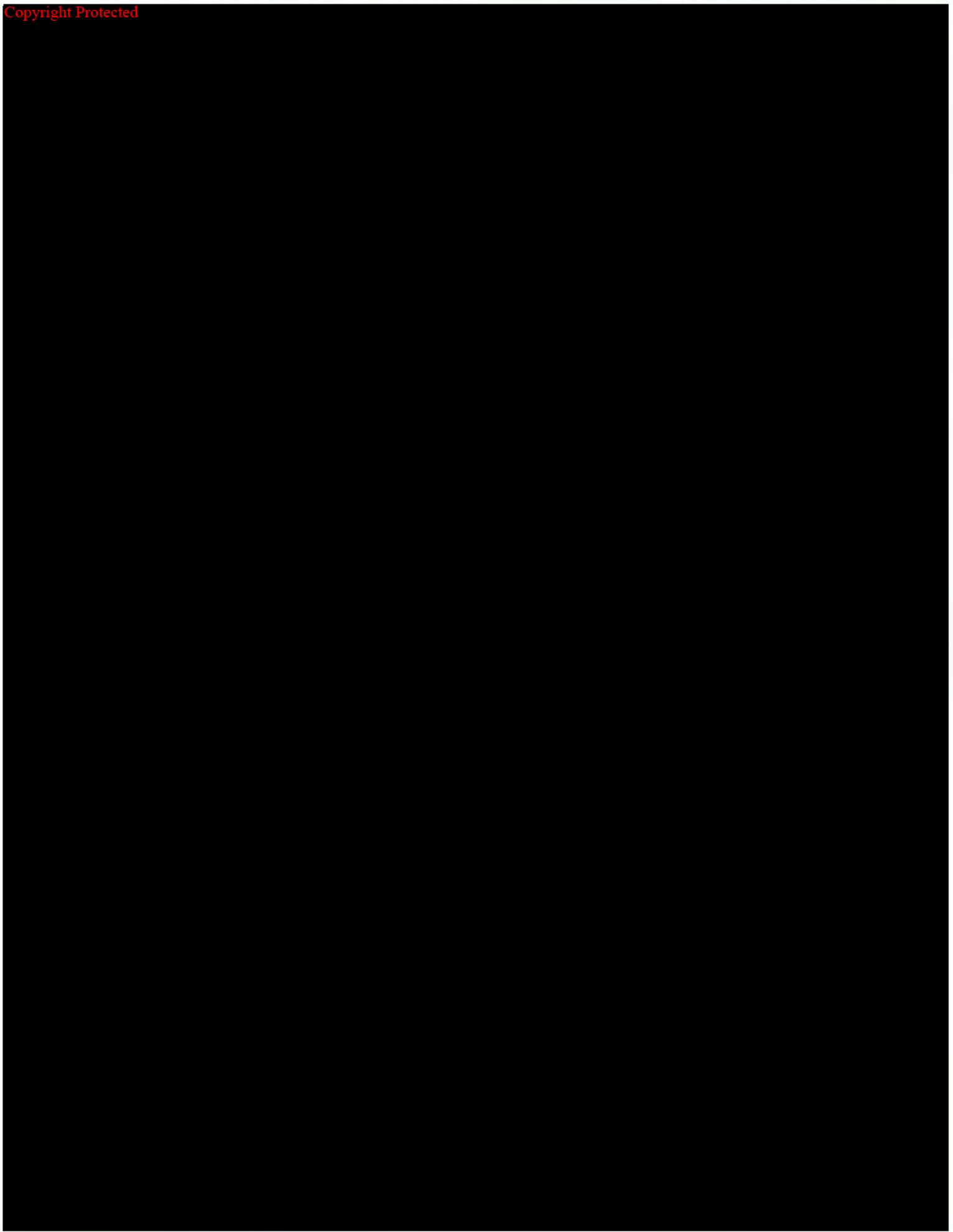
Objectives. The objective of the present paper is to review the main results of recent European cycle databases on ovulation detection and determination of the fertile window performed by the women themselves.

Methods. The ongoing German Long-term Cycle Database currently comprises 32 788 prospectively collected cycle charts of 1551 women, the I European Cycle Database (10 countries) 1328 women/19 048 cycles, the II European Cycle Database (six countries) 782 women/6724 cycles, and the World Health Organization Database (one European country) 234 women/2808 cycles. The women record cycle parameters (cervical mucus changes, temperature rise, etc.), family planning intention and sexual behavior.

Results. With the symptothermal method of natural family planning it has become possible to determine the fertile window in order to avoid pregnancy with a method effectiveness of 0.3%. According to a small sub-study, the ovulation time observed by the women themselves correlates closely with ovulation detected by ultrasound and measurement of luteinizing hormone (correlation within 1 day in 89% of the 62 cycles). Fertility awareness methods can be integrated into the management of sub-fertility. They seem to shorten the time to pregnancy.

Conclusions. Self-observation of the fertile window puts women into a position to develop a high level of reproductive competence that could be used much more in different areas than is currently the case.

Keywords: *Natural family planning, fertile window, efficacy, infertility, symptothermal method, ovulation detection*



[redacted]

Human Reproduction Vol.18, No.12 pp. 2628–2633, 2003

DOI: 10.1093/humrep/deg488

Estimated maximum failure rates of cycle monitors using daily conception probabilities in the menstrual cycle

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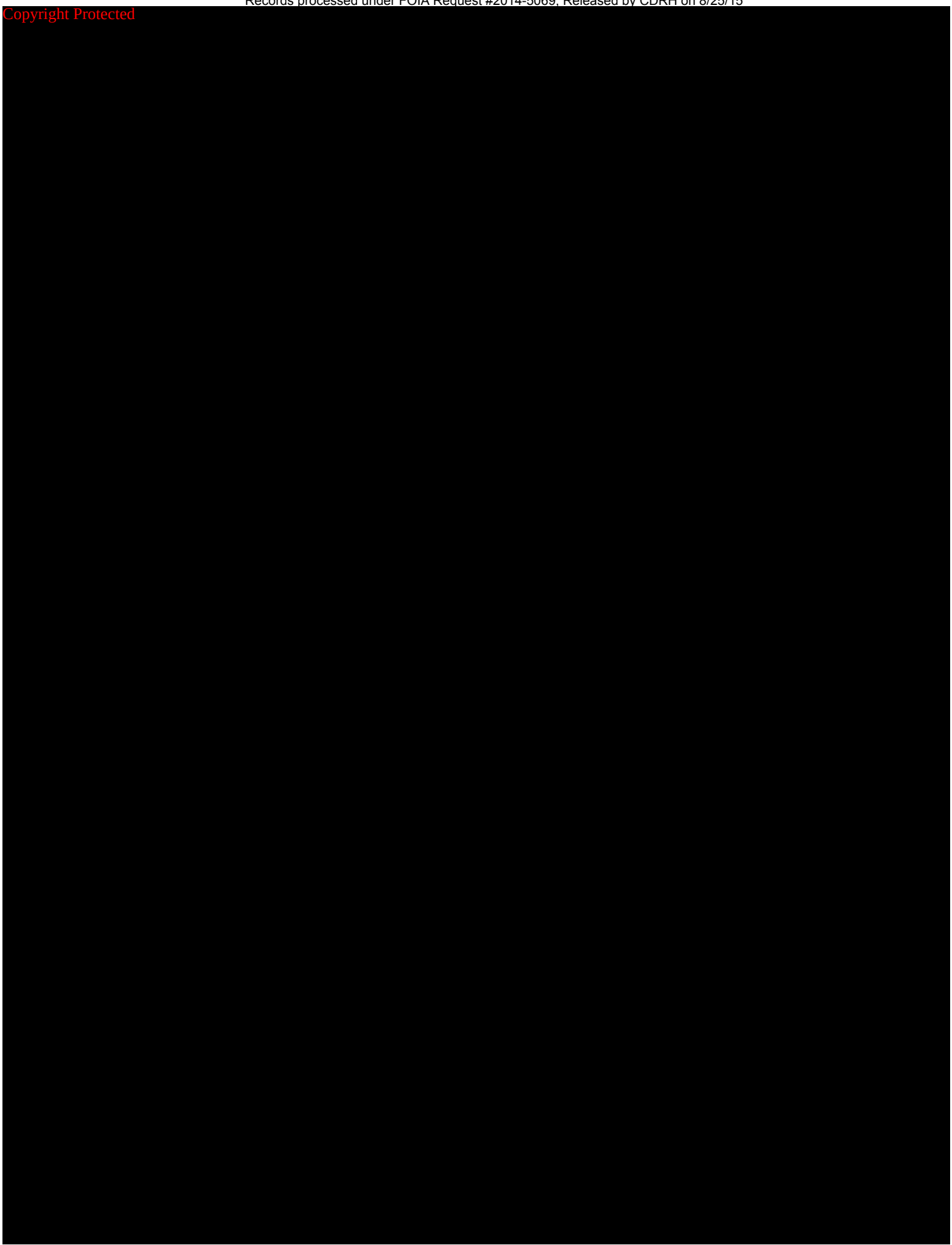
BACKGROUND: A number of menstrual cycle monitors have been developed to detect the fertile window of the menstrual cycle, mainly for contraceptive purposes. Reliable data on most of these systems are still missing but are urgently needed because many women use them and the tested systems differ enormously in price and effectiveness. We suggest a new efficacy estimating method to evaluate cycle monitors prior to full prospective clinical trials. METHODS: Sixty-two women prospectively tested seven cycle monitors and the symptothermal method (STM) of natural family planning (NFP) but not more than two different systems at the same time. The clinical fertile window was determined by detecting the day of ovulation using daily urinary LH measurements and daily ultrasonic folliculometry. This was compared to the fertile phase predicted by the systems. Maximum failure rates were estimated for each cycle monitor and the STM, using the daily conception probability rates taken from the European Fecundability Study. Intercourse was assumed to occur on each of all falsely predicted days of infertility. RESULTS: Sixty-two women with a mean age of 31 years (range: 21–42 years) contributed a total of 122 cycles to this study. Monitors based on the microscopic evaluation of saliva or mucus had many more false infertile days than the other methods based on temperature or hormonal measurements (225 versus 42 days). The maximum unintended pregnancy rates per cycle for temperature computers were estimated to be 0.0134–0.0336, for the hormonal computer 0.1155 and for mini-microscopes 0.2313–0.2369. For the STM of NFP, there were no false infertile days. CONCLUSIONS: The STM of NFP proved to be the most effective contraceptive method to detect the fertile window among all the methods tested. The estimated efficacy of the other cycle monitors range from the temperature computers (upper level) to the hormonal computer (medium level) and the mini-microscopes with very low estimated contraceptive efficacy.

Key words: cycle monitor/hormonal computer/mini microscopes/natural family planning/temperature computers



British Journal of Obstetrics and Gynaecology
July 1984, Vol. 91, pp. 685–689

Normal variation in the length of the luteal phase of the menstrual cycle: identification of the short luteal phase

ELIZABETH A. LENTON, BRITT-MARIE LANDGREN* &
LYNNE SEXTON *University Department of Obstetrics and Gynaecology, Jessop Hospital for Women, Sheffield and *Karolinska Institute, Stockholm, Sweden*

Summary. Normal probability plots were used to assess the homogeneity of a population of 327 luteal phases from apparently ovulatory menstrual cycles. The length of the luteal phase was defined as the interval (in days) following but not including, the luteinizing hormone peak, up to and including the day before onset of menstruation. A small sub-set of the population consisted of cycles with abnormally short luteal phases but the majority of the data followed a normal frequency distribution which gave a mean (± SD) for normal luteal phase length of 14·13 (± 1·41) days. It was estimated that all cycles with a luteal phase ⩽ 9 days were abnormal, and that 74%, 22% and 2% respectively of cycles with luteal phases of 10, 11 and 12 days were also abnormal. The total incidence of short luteal phases defined as above was 5·2%.

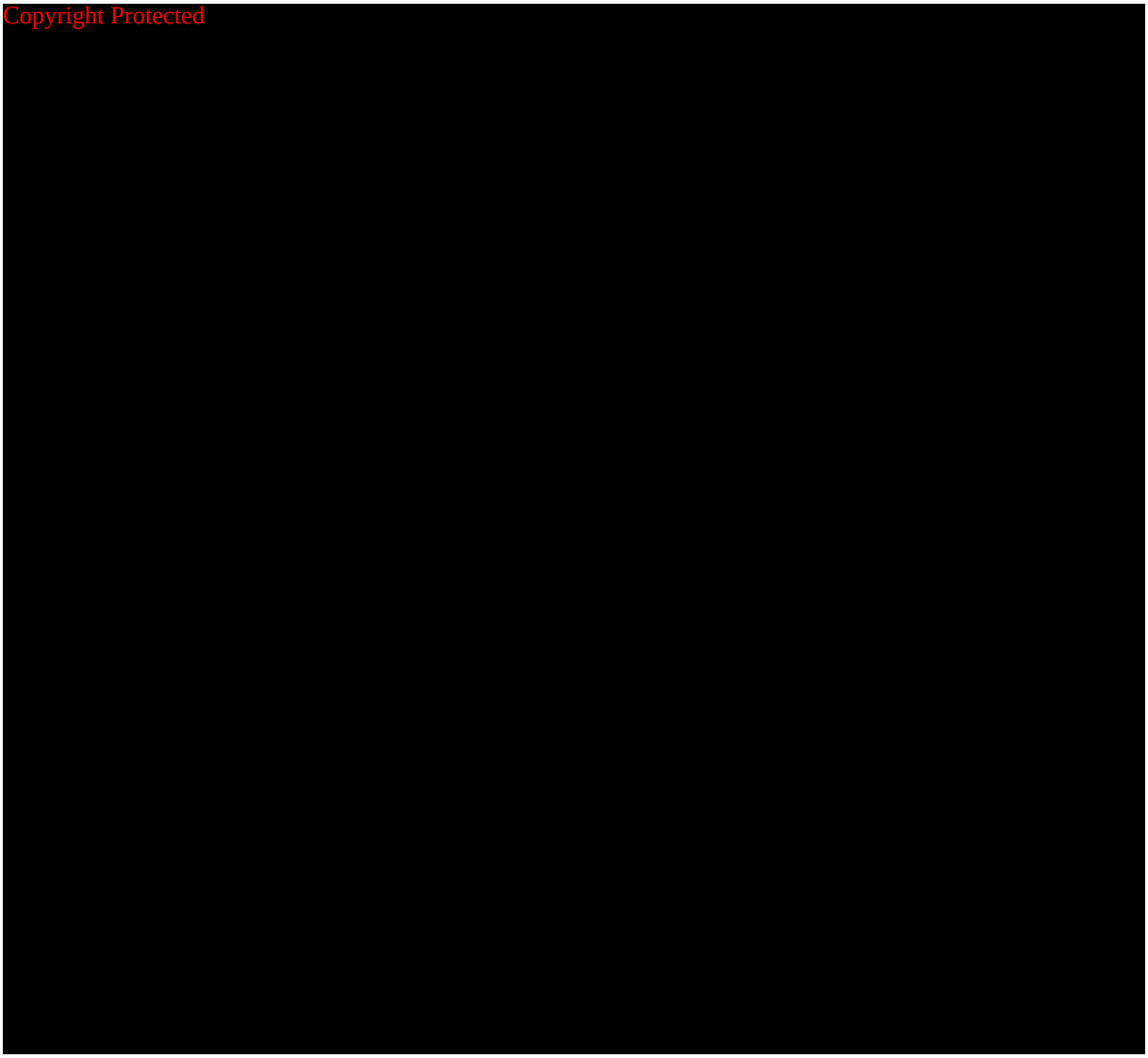
British Journal of Obstetrics and Gynaecology
July 1984, Vol. 91, pp. 681–684

Normal variation in the length of the follicular phase of the menstrual cycle: effect of chronological age

ELIZABETH A. LENTON, BRITT-MARIE LANDGREN,* LYNNE SEXTON & ROSEMARY HARPER *University Department of Obstetrics and Gynaecology, Jessop Hospital for Women, Sheffield and *Karolinska Institute, Stockholm, Sweden*

Summary. Normal probability plots were used to analyse the distribution of follicular phase length in a population of 293 apparently ovulatory menstrual cycles from women aged between 18 and 39 years. The length of the follicular phase was defined as the interval (in days) from the onset of menstruation up to, but not including, the day of the LH peak. Follicular phase length appeared to be log-normally distributed and graphical inspection of the probability plot suggested that the geometric mean (and 95% confidence limits) of follicular phase length in this study group was 12·9 (10·3 to 16·3) days. There was a significant decrease ($P<0·001$) in follicular phase length with chronological age, from 14·2 days in women aged 18–24 years to 10·4 days in women aged 40–44 years.

[redacted]



Cross sectional study of differences in coronary artery calcification by socioeconomic status

Helen M Colhoun, Michael B Rubens, S Richard Underwood, John H Fuller

ATTACHMENT Q1-1
REVISED INDICATION FOR USE STATEMENT

Indications for Use

510(k) Number (if known): K122337

Device Name: **OvuSense Advanced Fertility Monitoring System**

Indications For Use:

The OvuSense (OvuSense Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ AND/OR Over-The-Counter Use __X___

(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)

Page 1 of ___1__

ATTACHMENT Q1-2
REVISED 510(K) SUMMARY

510(k) Summary

This 510(k) summary of safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

DATE:	March 19, 2013
APPLICANT:	Fertility Focus Ltd. Robert Milnes, CEO Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW Tel: 044-1494-510272 Email: robert.milnes@fertility-focus.com
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION:	Penny Northcutt, RAC, FRAPS, CQA Regulatory Consultant for Fertility Focus REGSolutions, LLC Tel: 678-428-6978 Fax: 678-513-0937 Email: pennynorthcutt@theregsolutions.com
TRADE NAME:	OvuSense Advanced Fertility Monitoring System
CLASSIFICATION NAME:	Device, fertility diagnostic, proceptive
DEVICE CLASSIFICATION AND PRODUCT CODE:	Pre-amendment, Unclassified Product Code: LHD
PREDICATE DEVICE NAME:	Bioself 2000 Fertility Indicator, K904211

SUBSTANTIAL EQUIVALENCE:

The OvuSense Advanced Fertility Monitoring System is substantially equivalent to the legally marketed Bioself 2000 (K904211) ovulation monitor.

DESCRIPTION OF THE DEVICE:

The OvuSense Advanced Fertility Monitoring System is intended for measuring and recording core body temperature intra-vaginally on a nightly basis during the non-menstruating phases of the monthly female reproductive cycle. OvuSense consists of two components made of silicone

- a Personal Sensor, which collects the data, and a Reader (with LCD display), which establishes a communication link to the Personal Sensor whereupon the data is transferred to the Reader.

Electromagnetic induction communications hardware transmits the stored temperature data from the Personal Sensor to the receiving device, the Reader, activated when the Sensor is placed on the Reader cradle and the Reader's dedicated download button is pressed. The microprocessor based Reader filters the overnight data, then calculates and stores the 25th percentile value, representative of the average basal (lowest) overnight temperature.

The Reader then displays these nightly temperature readings on a graph using a relative scale – the key information for necessary calculations being the temperature changes relative to other recorded temperatures within a cycle for a particular user, and not absolute temperature value. At the start of the next cycle, indicated by the User inputting first day of the bleeding in the cycle, the Reader algorithm calculates the date of ovulation in the prior cycle, and uses this to predict the fertile period for the cycle which has just started. The Reader then displays fertility information in a verbal summary, including:

- An indication of the day ovulation occurred in the prior cycle, or if ovulation was not detected it displays this information instead.
- An indication whether the cycle length was within the expected normal parameters.

INTENDED USE/INDICATIONS FOR USE:
The OvuSense (OvuSense Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

TECHNOLOGICAL CHARACTERISTICS:
The OvuSense Advanced Fertility Monitoring System is substantially equivalent to the Bioself 2000 (K904211) medical device. They have the same intended use statement - used for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

They have the following similar and substantially equivalent technological characteristics:

a. Operating principles are the same for both devices - they are based on basal body temperature methods
b. Both devices use a thermistor sensor to monitor temperature
c. Both devices have the facility for user input of relevant data
d. Both devices have the facility for display of temperature graphs plus additional information on a user viewed screen
e. Both devices use software algorithms to calculate ovulation

The different but yet substantially equivalent technological characteristics of the OvuSense to the Bioself 2000 are:

a. External shape and dimensional specifications of the devices
b. Ergonomics of the user interface - The personal sensor of the OvuSense is inserted into the vagina for overnight wear during sleep and the Bioself 2000 fertility monitor personal sensor is only used in the vagina once upon waking up.

c. Number of temperature readings - The OvuSense takes continual temperature measurements during overnight wear whereas the Bioself 2000 records a single temperature measurement upon waking.
d. In addition, OvuSense has the capability of wireless communication of data from the vaginal temperature Personal Sensor to a Reader upon download.

The OvuSense Advanced Fertility Monitoring System has similar indications for use statement and the technological characteristics are functionally equivalent to the proposed predicate device, Bioself 2000. Any minor technological difference does not raise issues of safety and effectiveness. It is therefore concluded that the OvuSense Fertility Monitor is substantially equivalent to the existing marketed predicate devices.

NONCLINICAL PERFORMANCE TESTING:

A series of performance tests was conducted in support of the design verification of the OvuSense Advanced Fertility Monitoring System.

Summary of Performance Testing Conducted on OvuSense	
Biocompatibility	ISO Guinea Pig Maximization Sensitization Test
	ISO MEM Elution Assay
	ISO Mucosal (Vaginal) Irritation Test
	Physicochemical Extraction Testing
	ISO Acute Systemic Injection Test
	In Vitro Mouse Lymphoma Assay – 2 Extracts (ISO)
	In Vivo Mouse Micronucleus Assay – 2 Extracts
	Bacterial Mutagenicity Test (Ames Assay)
	Subchronic (14 day) Intravenous Toxicity Study in Non-Swiss Webster Mice (14 Repeat Dose Exposure)(GLP)
	Subacute (14 day) Intraperitoneal Toxicity Study in Non-Swiss Webster Mice (14 Repeat Dose Exposure) (GLP)
Electrical Testing	EN60601-1-4:2000 Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.
	EN60601-1-2:2007 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests
	EN301 489-3 v1.4.1 Electromagnetic Compatibility and Radio Spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3: Specific Conditions for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz
	IEC60601-1:2006 Medical equipment. Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
	EN302 291 v1.1.1 Electromagnetic compatibility and Radio spectrum Matters

510(k) Summary

Summary of Performance Testing Conducted on OvuSense	
	(ERM); Short Range Devices (SRD); Close Range Inductive Data Communication equipment operating at 13,56 MHz; Part 2: Harmonized EN under article 3.2 of the R&TTE Directive
Mechanical Testing	Tensile (Pull Test) Copyright Protected [redacted].
Design Verification & Validation	Physical Dimensions, User Cleaning, Reliability for Operating Life, Human Factors-Machine Interface
Cleaning Validation	Cleaning validation of Personal Sensor

CLINICAL TESTING:
Clinical investigation was conducted of the OvuSense – Advanced Fertility Monitoring System (AFMS) from 19 women who participated in a prospective study measuring 81 cycles over 3 months participation.

The data from the primary endpoint of the trial described in the CIP demonstrated that the AFMS system of ovulation detection provided a biological and statistically significant improvement in ovulation detection compared with the traditional method of oral temperature measurement. It demonstrated good linear agreement with the gold standard detection of ovulation using ultra-sound and an improved 95% confidence interval for the agreement.

CONCLUSION:
Based on the nonclinical verification performance testing and clinical validation, it can be concluded that the OvuSense Advanced Fertility Monitoring System is equivalent to the Bioself 2000 (K904211) with respect to intended use, principles of operation, and technological characteristics. The OvuSense Advanced Fertility Monitoring System has been demonstrated to be as safe, as effective, and performs as well as or better than the Bioself 2000 predicate.

ATTACHMENT Q1-3
OVUSENSE USER MANUAL

(b)(4) Old version User Manual

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ATTACHMENT Q3-1
PERSONAL SENSOR MSDS

(b)(4) Product Profile

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(b)(4) Material Safety Data sheet

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ATTACHMENT Q3-2
READER MSDS

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(b)(4) Certificate of Conformance

(b)(4) Statement of Biocompatibility

(b)(4) Certificate of Compliance

(b)(4) Certificate of Compliance

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(b)(4) Material Safety Data Sheet

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ATTACHMENT Q4-1
MAF AUTHORIZATION LETTERS

NuSil SILICONE TECHNOLOGY

Creative Partners in a Material World

25 January 2008

Dr. Mo Aslam
Technical Director
Fertility Focus Ltd
62 Brands Hill Avenue
High Wycombe
Bucks HP13 5PU

Dear Dr. Aslam:

This letter authorizes the Food and Drug Administration to include by reference, information in our device master file, (b)(4) [redacted].

The FDA has requested that you provide this letter with your submission and include a copy of this letter in any additional copies of your submission.

Sincerely yours,

(b)(4) [redacted]

NuSil SILICONE TECHNOLOGY

Creative Partners in a Material World

25 January 2008

Dr. Mo Aslam
Technical Director
Fertility Focus Ltd
62 Brands Hill Avenue
High Wycombe
Bucks HP13 5PU

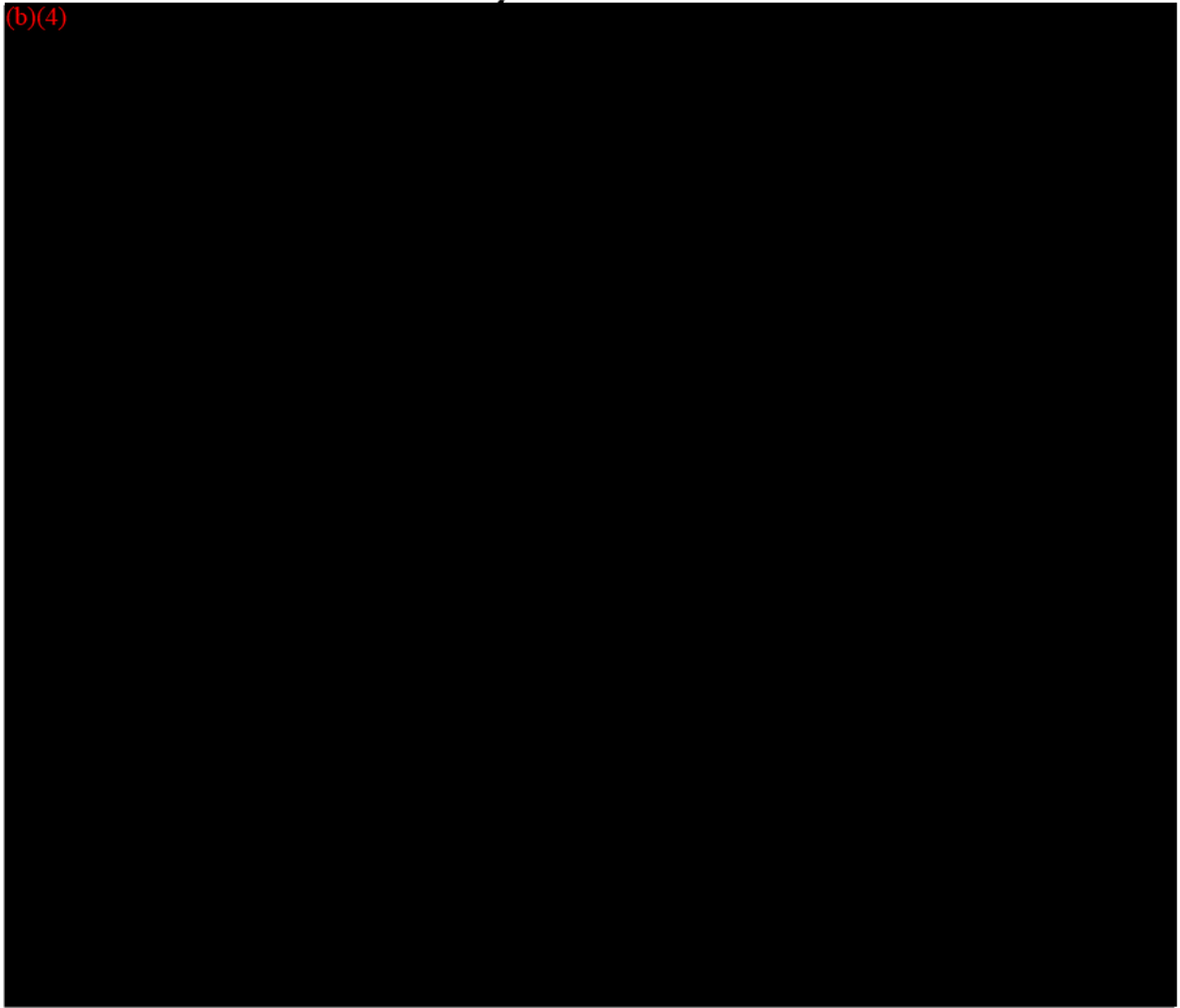
Dear Dr. Aslam:

This letter authorizes the Food and Drug Administration to include by reference, information in our device master file, (b)(4) elastomer.

The FDA has requested that you provide this letter with your submission and include a copy of this letter in any additional copies of your submission.

Sincerely yours,

(b)(4)



NuSil SILICONE TECHNOLOGY

Creative Partners in a Material World

25 January 2008

Dr. Mo Aslam
Technical Director
Fertility Focus Ltd
62 Brands Hill Avenue
High Wycombe
Bucks HP13 5PU

Dear Dr. Aslam:

This letter authorizes the Food and Drug Administration to include by reference, information in our device master file, (b)(4) [redacted]

The FDA has requested that you provide this letter with your submission and include a copy of this letter in any additional copies of your submission.

Sincerely yours,

(b)(4) [redacted]

ATTACHMENT Q7-1
SUMMARY OVUSENSE PERFORMANCE CHARACTERISTICS & FUNCTIONALITY INCLUDING ALGORITHM

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ATTACHMENT Q10-1
RISK ASSESSMENT MATRIX

(b)(4) Risk Analysis

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ATTACHMENT Q11-1
RISK MANAGEMENT PLAN, HAZARD IDENTIFICATION AND RISK MANAGEMENT REPORT

(b)(4) Risk Management

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ATTACHMENT Q11-2
SOFTWARE TRACEABILITY MATRIX

(b)(4) Traceability Matrix

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ATTACHMENT Q13-1
SUMMARY OF EMC AND SAFETY TESTING

(b)(4) Test Report

(b)(4) Test Report

(b)(4) Test Report

ATTACHMENT Q16-1
BIOCOMPATIBILITY TEST REPORTS

(b)(4) Test Report

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Appendix A: Individual Animal Data

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ATTACHMENT Q18-1
TENSILE TEST RESULTS

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ATTACHMENT Q19-1
OVUSENSE LINE DATA

(b)(4) Test Report

(b)(4) Data Information

(b)(4) Data Information

(b)(4) Data Information, (b)(4) CCI

(b)(4) Safety and Comfort Assessment

ATTACHMENT Q23-1
PERSONAL SENSOR AND READER REVISED LABELING

(b)(4) Old version User Manual

<table>
<tr><td>QUANTITY</td><td>1</td><td rowspan="2">OvuSense™ Sensor
To be used with OvuSense Reader. The OvuSense advanced fertility monitor is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating. OvuSense detects the presence and absence of ovulation, as well as predicting the fertile period for the next monthly cycle.</td></tr>
<tr><td>LOT
LOT CODE</td><td></td></tr>
<tr><td>SN
SERIAL NO.</td><td></td><td rowspan="4">Manufactured by:
a Fertility Focus Limited
Unit 19D, University of Warwick Science Park
Warwick Innovation Centre, Gallows Hill
Warwick CV34 6UW, United Kingdom
t +44 (0) 1793 848088
f +44 (0) 1793 855440
e service@fertility-focus.com
w www.fertility-focus.com

THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE

Conforms to ASTM E1113

fertility focus
M007-18OCT12-V2.0 USA</td></tr>
<tr><td>DATE OF MANUFACTURE</td><td>2012-07</td></tr>
<tr><td>USE BY</td><td>2014-07</td></tr>
<tr><td>SEE INSTRUCTIONS FOR USE</td><td>(b) EUROPEAN CONFORMITY</td></tr>
<tr><td colspan="2">STORE -20°C TO +50°C
MAX 95% RELATIVE HUMIDITY
(NON-CONDENSING)</td></tr>
</table>

ATTACHMENT Q25-1
STANDARDS DATA REPORTS

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 10993-3:2003 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-175	
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], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

[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 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		
SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED *		
DESCRIPTION		
JUSTIFICATION		
SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ 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 10993-11:2003 Biological evaluation of medical devices Part 11: Tests for systemic toxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2] ?	☒	☐
FDA Recognition number [3]	#2-176	
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: ISO 10993-12:2007: Biological Evaluation of Medical Devices -- Part 12: Sample preparation and referenc

[1] The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]

[2] Authority [21 U.S.C. 360d], http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

[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 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

STANDARD TITLE

CONFORMANCE WITH STANDARD SECTIONS*

SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ◆		
DESCRIPTION		
JUSTIFICATION		
SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ Yes ☐ No ☐ N/A
TYPE OF DEVIATION OR OPTION SELECTED ◆		
DESCRIPTION		
JUSTIFICATION		
SECTION NUMBER	SECTION TITLE	CONFORMANCE? ☐ 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.

ATTACHMENT Q26-1
SIGNED FDA 3674 FORM

See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 2-28-2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
Fertility Focus

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

3. ADDRESS *(Number, Street, State, and ZIP Code)*
Unit 19D, University of Warwick Science Park, Warwick Technology Park, Gallows Hill
Warwick, United Kingdom CV34 6UW

4. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) 044-1494-510272
(Fax)

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

OvuSense Advanced Fertility Monitoring System

Unclassified
Device, fertility diagnostic proceptive

Product Code: LHD

Personal Sensor: M011
Reader: M010

Starter Pack (Personal Sensor and Reader): M009

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
K122337

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)
(b)(4) [redacted]

12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
(Name) (b)(4) [redacted]
(Title)

13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*
Unit 19D, University of Warwick Science Park, Warwick Technology Park,
Gallows Hill
Warwick, United Kingdom CV34 6UW

14. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
(Tel.) (b)(4) [redacted]
(Fax)

15. DATE OF CERTIFICATION
Oct 22nd 2012

Form FDA 3674 (3/12) (FRONT)

PSC Publishing Services (301) 443-6740 EF

STATISTICAL DATA FOLDER
Q18 TENSILE TESTING RAW DATA

(b)(4) [redacted]

fertility focus

K122337/S002

July 30, 2013

US Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to FDA Questions to K122337, from FDA AI Dated April 12, 2013
OvuSense Fertility Monitoring System

Dear (b)(4)

Fertility Focus hereby submits additional clarification and documentation in support of the OvuSense K122337 under your review. We are addressing your questions dated April 12, 2013. Two paper copies and one eCopy were sent to the FDA Document Mail Center. The eCopy is an exact duplicate of the paper copy.

Your questions are in bold and Fertility Focus answers are in regular type face. Where a response includes an attachment, the attachment is labeled according to the question number. For example, Attachment Q3-1 would be Question 3 attachment 1.

Fertility Focus regards information provided in support of this Traditional 510(k) to be confidential and proprietary and afforded such protection under 21CFR 807.95 and other applicable statutes. We understand that the submission to the government of false information is prohibited by 18 U.S.C. 1001 and 21 U.S.C. 331(q). In accordance with the Safe Medical Devices Act of 1990, a 510(k) Summary of Safety and Effectiveness is included in this notification. A Premarket Notification Truthful and Accurate Statement has also been provided in this submission in accordance with 21 CFR 807.87(j).

We trust this additional clarification meets your needs to complete the review of the Fertility Focus 510(k) K122337. If there are any questions, please contact me at 678-428-6978 (phone) or email to pennynorthcutt@theregsolutions.com for interactive review.

Sincerely,

Penny Northcutt

Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

July 30, 2013

US Food and Drug Administration
Center for Devices and Radiological Health
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10903 New Hampshire Avenue
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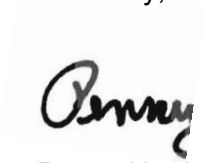
Sincerely,



Penny Northcutt, RAC, FRAPS, CQA
Regulatory Consultant and Official Correspondent for Fertility Focus
Executive Director, REGSolutions, LLC

RESPONSE TO FDA QUESTIONS OF APRIL 12, 2013
OVUSENSE FERTILITY MONITORING SYSTEM

CONTENTS

Page No.

ATTACHMENTS

TABLES

1. **As indicated in the original submission, an epoxy coating material (Thermistor) that has direct contact with the vagina is used in the personal Sensor. However, in Table Q3-1 provided in your Supplement 1, this material is not included. Please provide safety information on Thermistor (e.g., Certificate of Analysis and/or Material Safety Data Sheet).**

(b)(4)

The understanding that this is an element in direct contact with the vagina is assumed to be derived from FDA's review of page 42 of the original submission, OvuSense Advanced Fertility Monitoring System Materials. In the "Patient Contact" column against (b)(4) (b)(4) it states "Direct." This is an incomplete statement. The Sensor has direct contact with the vagina but the Thermistor and its constituent materials are attached to the Printed Circuit Board contained within the Personal Sensor and as such all constituent materials are completely and entirely encased by the Personal Sensor outer shell and therefore have NO direct contact with the vagina.

No part of the Thermistor device or its constituent materials is in direct contact with the vagina.

See **Attachment Q1-1** for the Thermistor data sheet.

2. In response to Question 4b from our October 5, 2012 letter, you provided an estimated amount of the colorant (b)(4) used in each device. Please clarify the amount (in weight) of (b)(4) used in each personal Sensor that has direct contact with the vagina.

Please note that following the material prototyping phase at the manufacturer of the Personal Sensor, the (b)(4) colorant was replaced with (b)(4) colorant due to manufacturing efficiencies.

(b)(4) was erroneously left in the original Bill of Materials and therefore submitted in error in Attachment C – Materials Information of the original submission. There is therefore no (b)(4) used in the manufacture of the Personal Sensor. Fertility Focus apologizes that this was not made completely clear in the re-submission of March 19, 2013.

See **Attachment Q2-1** for the (b)(4)

For the avoidance of doubt, all biocompatibility testing presented in the original 510K submission, the first AI response and now in this response were carried out on this M(b)(4) colorant.

3. **In response to Question 4d from our October 5, 2012 letter, you stated there is no toxicity risk in the colorant based on the result of biocompatibility testing.**

   The Personal Sensor is used during the non-menstruating phases of the reproductive cycle (typically 21 days) (b)(4) . If the colorant (b)(4) used in the Personal Sensor is leachable, it may pose some potential risks (e.g., carcinogenesis) that are not evaluated by the biocompatibility testing conducted on this device component. Therefore, we continue to recommend that you conduct a toxicity risk assessment of this colorant that is preferably based on its eluted amount of colorant from the Sensor under intended use, instead of the absolute total amount of the colorant used in the device. FDA would be willing to aid in the review of your protocol prior to initiating testing.

Note information on (b)(4) colorant provided in answer to Q2 above.

As FDA requested, Fertility Focus has conducted (b)(4)

Fertility Focus further commissioned (b)(4) The extensive testing (beyond the requirements requested in FDA AI Dated April 12, 2013) shows the OvuSense Personal Sensor is well within the calculated Margin of Safety for all (b)(4) , and the OvuSense Personal Sensor is not expected to produce any unacceptable health risks.

See **Attachment Q3-1** for the (b)(4)

4. Information provided in response to Question 7 from our October 5, 2012 letter indicates that between download and data filtering, the data recovery function will identify (b)(4) to download. Please explain why such a big window of data is used, including what appears to be (b)(4) (after placing the Sensor in the cradle).

A (b)(4) is employed in order to ensure a full night's data is collected.

Although the user is instructed to remove the Personal Sensor from the vagina each morning, wash the Sensor, place the Sensor on the cradle of the Reader and then press the Download button, the Reader software has to account for a potential delay between removal of Sensor and pressing of the Download button.

The (b)(4), maximizing the chances that a typical (b)(4) can still be successfully downloaded between removal of the Personal Sensor and pressing of the Download button even there is a delay. In the case that a Download occurs immediately after removal of the Sensor then, (b)(4)

As described in section 16.1 of Attachment Q7-1 of our Response to AI Questions dated March 19, 2013, (b)(4) is the first of a number of steps employed by the Reader to (b)(4).

As is also described in section 16.1 of Attachment Q7-1 of our Response to AI Questions dated March 19, 2013, (b)(4) is also employed to allow for the eventuality of collecting (b)(4) collection of a full night's data even if the user has an irregular sleep pattern, and/ or presses the Download button with a delay following removal of the Sensor after overnight use.

Also, will temperatures be collected post-removal during Sensor washing in hot water? If so, please explain why this does not cause the inclusion of erroneous data in basal body temperature (BBT) calculations.

Yes all temperature data (b)(4) are captured. However,

a. The Personal Sensor has a maximum temperature cut-off of (b)(4) Please see answer to question 6.
b. (b)(4)

(b)(4)

d. The algorithm then further (b)(4) as described in section 16.5.1 of Attachment Q7-1 of our Response to AI Questions dated March 19, 2013, so, (b)(4)
(b)(4)
e. The algorithm then requires (b)(4) of this (b)(4)

In summary, with this (b)(4)
(b)(4)

5. The information provided (including the user manual) does not specify if there is a limit on the number of hours a user can sleep/collect data. Given that the algorithm identifies a (b)(4), please clarify whether there is a limit on the number of hours of data that can be collected in a single day and provide viable data for that day.

Due to the (b)(4) . However, the recorded data must fall completely (b)(4)

Page 3 of Attachment P – OvuSense Personal Sensor Temperature Tests in the original submission shows the target settling time to normal body temperature (b)(4) (b)(4) Section 16.2 of Attachment Q7.1 of our response of 19th March 2013 discusses the f(b)(4) conducted by the OvuSense Reader algorithm and explains that the (b)(4) .

With regards to data collection, due to the fact the data are (b)(4) (b)(4) , there is no requirement to indicate a maximum overnight usage to the user unless they regularly insert and retain the Sensor (b)(4)

For the purposes of clarity, Fertility Focus has added a Nightly Usage section in the User Manual indicating the minimum and maximum number of hours Sensor usage is required for any single night.

(b)(4)

Below is text from page 4 of the User Manual:

Nightly Usage: The Sensor is designed only for use when you are sleeping, and should be removed during waking hours. It requires a minimum of two hour's usage at night to calculate a valid result for that night, and will use a maximum of 14 hours information from a single night, although it can be left in for longer if you happen to sleep beyond 14 hours. If you miss a night, do not worry. Simply insert the Sensor on the subsequent night and continue usage.

6. In response to Question 8 of our October 5, 2013 letter, you indicated that (b)(4) . You also indicate that (b)(4) will be discarded. Please clarify if there is any (b)(4) (b)(4)

The Sensor calibration table sets output values using the (b)(4)

In the Sensor calibration table (Table Q6-1) example below, the (b)(4) any ADC values above 3150 are automatically set to the maximum value of 42.0°C.

The second half of the answer to Question 4 explains (b) and calculations performed by the algorithm in order to calculate a BBT value.
It can be seen from that explanation, and the Sensor calibration description contained here that it is almost impossible for rapid fluctuations or constant biologically improbable temperatures to induce spurious results. It is equally almost impossible for fluctuations or constant false temperatures induced by exposure to other heat sources to induce spurious results.

If, even after all these steps, (b)(4)

Table Q6-1: Example ADC Output

(b)(4)

7. According to the manual, the operating environment is 16°C to 40°C. Please identify the maximum temperature that the Sensor can withstand during operation.

The operating environment of 16°C to 40°C refers to the Reader part of the OvuSense product only. The maximum temperature for the Sensor is 50°C (-4.0°F to 120.0°F).

Fertility Focus has clarified the operating environment on page 7 in the User Manual. See **Attachment Q7-1** for an updated OvuSense User Manual.

Operating Environment
The OvuSense Reader must be operated in an environment of 16°C to 40°C (60.8°F to 104.0°F) and in a relative (non condensing) humidity of 15% to 95%. The OvuSense Sensor can be operated in an extreme environment of -20°C to 50°C (-4.0°F to 120.0°F) in a relative (non condensing) humidity of 15% to 100%, but will discard temperature values recorded below 36.0°C (95.9°F) and ignores temperatures above 42.0°C (107.6°F).

8. Based in your original submission and Supplement 1, we understand that the proposed device has the following design and technology features:

- **Two separate components: Personal Sensor (for data recording) and Reader (for data analysis)**
- **Overnight, continuous recording of BBT by Personal Sensor**
- **Wireless transfer of data from Personal Sensor to recorder**
- **Algorithm to determine BBT**

You have identified the Bioself 2000 Fertility Indicator (K904211) as the predicate device. However, this predicate does not have any of the above features, but the DuoFertility that was cleared under K102499 does. Therefore, we recommend you remove Bioself 2000 from this submission and identify the DuoFertility as the predicate device. Please provide a new Substantial Equivalence Discussion regarding the Indications for Use and technology (e.g., features, materials, principle of operation, etc.). Please include an analysis of why any differences between the subject and predicate devices do not render the device Not Substantially Equivalent (e.g., any differences in technological characteristics are accompanied by information that demonstrates the device is as safe and effective as the predicate and do not raise different questions of safety and effectiveness than the predicate), affect safety or effectiveness, or raise different questions of safety and effectiveness (see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)).

As FDA advises, we have added the DuoFertility Monitor (K102499) as a predicate device for OvuSense.

We also respectfully wish to continue with Bioself 2000 Fertility Indicator (K102499) as a predicate device as both OvuSense and Bioself 2000 measure basal body temperature (BBT) via a vaginal probe (which DuoFertility does not) and both use a software algorithm to predict a woman's ovulation pattern.

See **Attachment Q12-2** for a revised 510(k) Summary.

SUBSTANTIAL EQUIVALENCE DECISION-MAKING PROCESS

The Fertility Focus OvuSense Fertility Monitor is substantially equivalent to the DuoFertility Monitor (K102499). Both the OvuSense Fertility Monitor and DuoFertility have similar indications for use, principles of operation-basal body temperature reading, technological characteristics-electronic and software driven, and substantially equivalent device designs.

The 510(k) "Substantial Equivalence" Decision-Making Process in ODE Guidance Document #K86-3, *Guidance on the CDRH Premarket Notification Review Program*, was used to determine substantial equivalence. Answers to the relevant questions lead to a determination of substantial equivalence, as follows:

1. DOES THE DEVICE HAVE SAME INDICATION STATEMENTS ..... YES

The FDA cleared DuoFertility Monitor and the Fertility Focus OvuSense statements are **substantially equivalent**.

The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

The DuoFertility Monitor is intended for measuring, and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

2. DOES NEW DEVICE HAVE THE SAME TECHNOLOGICAL CHARACTERISTICS, E.G., DESIGN, MATERIALS, ETC.? ..... YES

OvuSense and DuoFertility Monitor have the following similar and substantially equivalent technological characteristics:

- Operating Principle – Both devices assess Basal Body Temperature.
- Temperature Sensor – Both devices use thermistor sensors.
- Sensor Accuracy – The DuoFertility device has a quoted accuracy of +/- 0.05 degrees Centigrade (in 510(k) summary predicate device comparison), and of +/- 0.1 degrees Celsius (in Specific Claims section of currently available device User Manual http://www.duofertility.com/files/marketing_docs/User-manual.pdf); OvuSense has an accuracy of +/- 0.05 degrees Centigrade (Attachment P "OvuSense Personal Sensor Temperature Tests" of original submission). Any potential difference in the accuracy of temperature measurements is not believed to raise any issues of safety, and is a function of the requirements of each devices' algorithms.
- User Inputs – Both devices have the facility for user input of relevant data.
- Display of Graphs – Both devices have the facility for the display of temperature graphs. The DuoFertility device uses a computer for this display and uses an absolute temperature scale, whilst OvuSense uses the OvuSense Reader for display and a relative temperature scale. The different display methodologies do not raise any safety issues, with the relative temperature scale allowing the OvuSense user a graph view optimized to their particular temperature readings (as explained in more detail in section 9 of "Summary OvuSense Performance Characteristics & Functionality including Algorithm," page 348 of response of March 19, 2013).
- Number of Measurements – Both devices record multiple temperatures. The difference in any relative number of temperature measurements is not believed to raise any issues of safety, and is simply a function of the requirements of each devices' algorithms.
- Automatic measurements – Both devices take measurements automatically.
- Wireless transfer of data – Both devices involve the transfer of data from the Sensor to a receiving unit.

- Algorithm – Both devices use an algorithm to calculate the date of ovulation. The additional information provided by the OvuSense device in respect of absence of ovulation and fertile period prediction is not believed to raise any direct issues of safety, and is employed for increased effectiveness.

The following differences between DuoFertility and OvuSense are noted and thus a secondary predicate or reference device – Bioself 2000 (as employed in the OvuSense original submission) is used for substantial equivalence purposes.

- Number of Thermistors – The DuoFertility device uses two thermistors plus an accelerometer/movement sensor; the OvuSense device uses a single thermistor. The Bioself 2000 device uses a single thermistor.
- User Wearing Location – The DuoFertility device is worn on the skin; the OvuSense device is placed intravaginally by means of a Personal Sensor. The Bioself 2000 device can be used intravaginally or orally.

The use of two thermistors and an accelerometer (in DuoFertility) versus the use of a single thermistor (OvuSense and Bioself 2000) is not believed to raise any direct issues of safety or effectiveness, and the relative location of vaginal versus skin placement is employed by OvuSense and Bioself 2000.

The FDA cleared DuoFertility device and the Fertility Focus OvuSense device as well as the Bioself 2000 (for the described elements above) have technological characteristics that are **substantially equivalent**.

3. ARE THE DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH TO ENSURE EQUIVALENCE? .... YES

A complete descriptive matrix of the device characteristics for the Fertility Focus OvuSense as compared to the predicate device DuoFertility (K102499) is shown in Table Q8-1. This information demonstrates the **substantial equivalence** between the Fertility Focus OvuSense and the predicate DuoFertility (K102499) with the Bioself 2000 (K904211).

4. ARE PERFORMANCE DATA AVAILABLE TO ASSESS EQUIVALENCE? ..... YES

5. DOES THE PERFORMANCE DATA DEMONSTRATE EQUIVALENCE? ..... YES

The verification testing performed for the Fertility Focus OvuSense Fertility Monitor demonstrates that the device performs as intended. The OvuSense Fertility Monitor complies with the requirements of ASTM E1112:2011 Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature. Electrical testing all passed as demonstrated in Section 9 of the original Submission. Software level of concern is Minor and evidence of software testing is included in Section 5 of the original Submission.

The Fertility Focus OvuSense performs (in use) identically to the predicate ovulation monitor in all respects except for the vaginal placement of the Sensor. Fertility Focus OvuSense is demonstrated to be **substantially equivalent** to the DuoFerility Monitor

(K102499) predicate device. The Bioself (K904211) also has an intended use for vaginal placement.

Clinical testing was performed as validation that Fertility Focus OvuSense Fertility Monitor performs as the user expects. Comparisons were made to ultrasound detection as the gold standard for predicting the fertility cycle.

Performance testing does not raise any new questions with regards to safety or effectiveness when compared to the predicate device.

See Section 8 “Summary of Performance Testing” of the Original Submission for a summary of the testing performed, and additional information supplied in the response of March 19, 2013.

6. REASON FOR PREMARKET NOTIFICATION?

To obtain clearance for the new Fertility Focus OvuSense Fertility Monitor, as described in detail in Section 4 of the original Submission.

Substantial Equivalence

The Fertility Focus OvuSense Fertility Monitor is substantially equivalent to the DuoFertility Monitor (K102499). The Bioself 2000 (K904211) device is intended use has an intended use for vaginal placement. The OvuSense Fertility Monitor has similar indications for use statements, principles of operation, and technological characteristics as the predicate devices. Table Q8-1 presents the similarities and differences.

Table Q8-1: Predicate Equivalence Matrix

	Feature	Fertility Focus OvuSense (K122337) Proposed Device	DuoFertility Monitor (K102499) Predicate Device	Supporting Documents
General	Equivalent Statement	The Fertility Focus OvuSense Fertility Monitor is substantially equivalent to the DuoFertility (K102499) ovulation monitor. The Fertility Focus OvuSense Fertility Monitor has similar indications for use statements, principles of operation, and technological characteristics as the predicate device.		See Section 4 in the original Submission for details
	510K Reference	K122337	K102499	Same See **Attachment Q8-1** for Predicate Device Information
	Manufacturer	(b)(4) [redacted]	Cambridge Temperature Concepts Ltd, UK	
	Product Trade Name	Fertility Focus OvuSense Fertility Monitor	DuoFertility Monitor	
	Classification #	Unclassified	Unclassified	
	Classification Name	Device, fertility diagnostic, proceptive	Device, fertility diagnostic, proceptive	
	Product Code	LHD	LHD	

Table Q8-1: Predicate Equivalence Matrix				
	Feature	**Fertility Focus OvuSense (K122337) Proposed Device**	**DuoFertility Monitor (K102499) Predicate Device**	**Supporting Documents**
Labeling	Indications for Use Statement	The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).	The DuoFertility Monitor is intended for measuring, and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).	Substantially Equivalent See **Attachment Q8-1** for Predicate Device Information
	Patient Population/ Environment of Use	Home use by a woman who has menstrual cycles and is interested in her ovulation pattern. OTC device.	Home use by a woman who has menstrual cycles and is interested in her ovulation pattern. OTC device.	Substantially Equivalent See **Attachment Q8-1** for Predicate Device Information
Device Description	Device Description	The OvuSense Fertility Monitor consists of a Personal Sensor and a Reader (with LCD display). The Personal Sensor records temperature collected from the vagina continuously throughout the night.	The DuoFertility system is a computerized basal body temperature thermometer with the following features: • A temperature Sensor with integrated data logger to monitor temperature throughout sleep and store the temperature readings. • Adhesive patches to hold the temperature Sensor against the user's skin.	Substantially Equivalent See **Attachment Q8-1** for Predicate Device Information

Table Q8-1: Predicate Equivalence Matrix				
	Feature	**Fertility Focus OvuSense (K122337) Proposed Device**	**DuoFertility Monitor (K102499) Predicate Device**	**Supporting Documents**
	Principles of Operation	Measures basal body temperature via vagina in (b) (4) overnight, during the non-menstruating period of a woman's cycle.* Uses the data and applies a software algorithm to calculate the start and end of the fertile phase.	Measures basal body temperature via skin sensor using multiple measurements. Uses a software algorithm to calculate the date of ovulation.	
	Sensor	Single thermistor sensor.[1] Measuring accuracy within ± 0.05 degrees Centigrade. Placed intravaginally by means of Personal Sensor.[2]	Two thermistor sensors plus an accelerometer/movement sensor. Measuring accuracy within ± 0.05 degrees Centigrade. Worn on the skin.	

[1] Secondary predicate or reference device Bioself 2000 uses a single thermistor
[2] Bioself 2000 can be used intravaginally or orally

Table Q8-1: Predicate Equivalence Matrix				
	Feature	**Fertility Focus OvuSense (K122337) Proposed Device**	**DuoFertility Monitor (K102499) Predicate Device**	**Supporting Documents**
	Display and Measurement	The OvuSense Reader has an LCD display that shows level of fertility, and five buttons for the user to interact with the Reader. The LCD display shows user input data and fertility/ovulation information. Automatically records multiple temperature measurements. Fertility prediction is calculated by software algorithm and displayed to user on LCD screen of Reader. Data is displayed as specific range of days for fertility, as well as a graph. Displays fertility information for up to past three menstrual cycles. Reader displays graph of fertility using a relative temperature scale.	Microprocessor based Reader to process and display temperature readings and fertility information. Automatically records multiple temperature measurements. Fertility prediction is calculated by software algorithm and shown on a scale to the user with use of varying shades of green to indicate fertile period is imminent. Uses a computer for graph display of fertility using an absolute temperature scale.	
	Data Transfer	Data is transferred wirelessly from the Sensor to the Reader (receiving unit).**	Radiofrequency communications hardware to transmit the stored temperature data to a receiving device.	

Table Q8-1: Predicate Equivalence Matrix				
	Feature	**Fertility Focus OvuSense (K122337) Proposed Device**	**DuoFertility Monitor (K102499) Predicate Device**	**Supporting Documents**
	User Interaction	User interacts with menus/prompts displayed on LCD screen via five buttons on Reader device.	User interacts with device via buttons on device and PC software.	
Device Construction	Materials	Reader: Plastic casing Personal Sensor: Silicone casing	Reader: Plastic casing Sensor: Attached to skin using supplied "adhesives"	Substantially Equivalent See Attachment C of original Submission and **Attachment Q2-1** (of this response) for OvuSense Materials Information, and **Attachment Q8-1** for Predicate Device Information
	Power Supply	120V a/c connector	Charging of unit via PC connected USB cable	No new questions of Safety and Effectiveness See Section 8 of original Submission for Performance Testing
	Battery	Rechargeable internal 9VDC battery	Battery life of the sensor is estimated to be 3 to 6 months and the battery cannot be replaced	
Sterilization & Other	Packaging	Personal Sensor in Tyvek pouch, shipping carton	Shipped in DuoFertility box	No new questions of Safety and Effectiveness See Section 8 of original

Table Q8-1: Predicate Equivalence Matrix				
	Feature	**Fertility Focus OvuSense (K122337) Proposed Device**	**DuoFertility Monitor (K102499) Predicate Device**	**Supporting Documents**
	Sterilization	Non-Sterile	Non-Sterile	Submission for Performance Testing
	Biocompatibility	Materials have been assessed based on ISO 10993-1:2003	Materials have been assessed based on ISO 10993-1:2003	See Attachments D, E, F, and G of original Submission, Attachment Q16-1 of March 19, 2013 response, and **Attachment Q3-1** and **Q3-2** (in this response) for Fertility Focus Biocompatibility Testing

Other reference devices for OvuSense which are legally marketed with substantially equivalent attributes as OvuSense are:

*Bioself K904211 (reference device for vaginal use and contains one thermistor as does the OvuSense)

**VitalSense K033534 (reference device for wireless or remote data download)

9. **The dosage volumes of test samples used in your (b)(4) Please note that per ISO 10993-11, the maximum dosage volume for both intravenous and intraperitoneal administration of test sample in the systemic toxicity study is 50 ml/kg for mice. Accordingly, we have recommended that an injection dose of 50 ml/kg for mice is used in systemic toxicity studies. Therefore, please address the following issues:**

   a. **Please provide the results of the Subchronic (14 day) Intravenous Toxicity Study assessed at 50 ml/kg to support the Personal Sensor.**
   b. **Please confirm whether a dosage volume (b)(4)**

See **Attachment Q9-1** for a response to the Agency's questions from (b)(4), dated April 16, 2013, in regards to the intravenous and intraperitoneal dosage administration.

(b)(4)

10. In response to Question 18 from our October 5, 2012 letter, you conducted (b)(4) . You indicated that (b)(4)

As discussed with (b)(4) in interactive review he agreed the below rationale (b)(4) .

(b)(4)

11. On page 5 of your cover letter to Supplement 1 you list several reasons why OvuSense provides accurate readings. One reason you cite is "the vagina is much closer to the site of thermogenic action of progesterone on the ovary – i.e. the site where the temperature rise associated with ovulation occurs-than alternative oral temperature based methods." Please clarify whether you are asserting that the rise in basal body temperature associated with luteinizing hormone surge is due to temperature rise on the ovary per se, as opposed to the release of ovarian hormones into the circulation (e.g. progesterone metabolites) that result in a rise in basal temperature. The reason this is important is that FDA considers that this device may be misbranded if you claim that vaginal location of the OvuSense Personal Sensor is superior to other locations for taking temperature readings by virtue of the proximity of the upper vagina to the ovaries.

The clinical trials data provided in the OvuSense submissions show its superior accuracy in comparison to oral temperature measurement. Fertility Focus asserts that the vaginal location of the OvuSense Personal Sensor is indeed key to the superior accuracy associated with the device. However, this is due (along with the other elements outlined in the list on page 5 of Supplement 1) to (b)(4) [redacted].

No specific claim is being asserted by this response with respect to proximity to temperature changes on the ovary, no literature accompanying the device includes this sentence, and we will not advertise in this manner.

12. The device name identified on the 510(k) Cover Sheet and Indications for Use form is OvuSense. However, this device is also identified as the OvuSense Advanced Fertility Monitoring System in 510(k) Summary and Labeling. Please use the same device name throughout your submission. We recommend that you remove the term "Advanced" because this is a claim that would need to be supported by research data.

Fertility Focus has removed the term "Advanced" from the device name. These documents have been updated to reflect the changes requested by the Agency.

See **Attachment Q7-1** for an updated OvuSense User Manual.

See **Attachment Q12-1** for a revised Indication for Use Form.

See **Attachment Q12-2** for a revised 510(k) Summary.

See **Attachment Q12-3** for revised OvuSense labeling.

13. Please provide an updated version of your 510(k) Cover Sheet (Form 3514) and 510(k) Summary reflecting your responses to this letter. Please be advised that the 510(k) Summary should include a high level description of your device and testing per 21 CFR 807.92. We recommend that you refer to the following website for content to include in a 510(k) Summary:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYour Device/PremarketSubmissions/PremarketNotification510k/ucm14265l.htm

Please note that additional changes may need to be made upon review of the revised Summary.

These documents have been updated to reflect the changes requested by the Agency.

See **Attachment Q12-2** for a revised 510(k) Summary.

See **Attachment Q13-1** for revised 510(k) Cover Sheet (FDA Form 3514) and Consensus Standards forms (FDA Form 3654).

14. In response to Question 23b from our October 5, 2012 letter, you updated your carton box labels by adding "Date of Manufacture" and "Use By." It appears that you have proposed a 2-year shelf-life claim for your device. However, you have not provided data to show that the Personal Sensor (b)(4) Therefore, please assess battery life of the Personal Sensor to propose a more accurate shelf-life for this component. The analysis should address temperatures between -20°C and +50°C (storage conditions). Please replace "Use By" with "Date of Expiration" on carton box labels.

See **Attachment Q14-1** Power Measurements for the OvuSense Sensor. The conclusion of this report is:

(b)(4)

See **Attachment Q12-3** for revised OvuSense labeling.

15. In Supplement 1, you modified your Indications for Use statement. However, you did not update your 510(k) Summary and labeling accordingly. Please revise your 510(k) Summary, carton labels and User Manual by including the updated Indications for Use statement.

Please be advised that we may request additional edits to the device labeling after review of your additional information.

We have revised our Indications for Use statement in the following documents.

See **Attachment Q7-1** for an updated OvuSense User Manual.

See **Attachment Q12-1** for a revised Indication for Use Form.

See **Attachment Q12-2** for a revised 510(k) Summary.

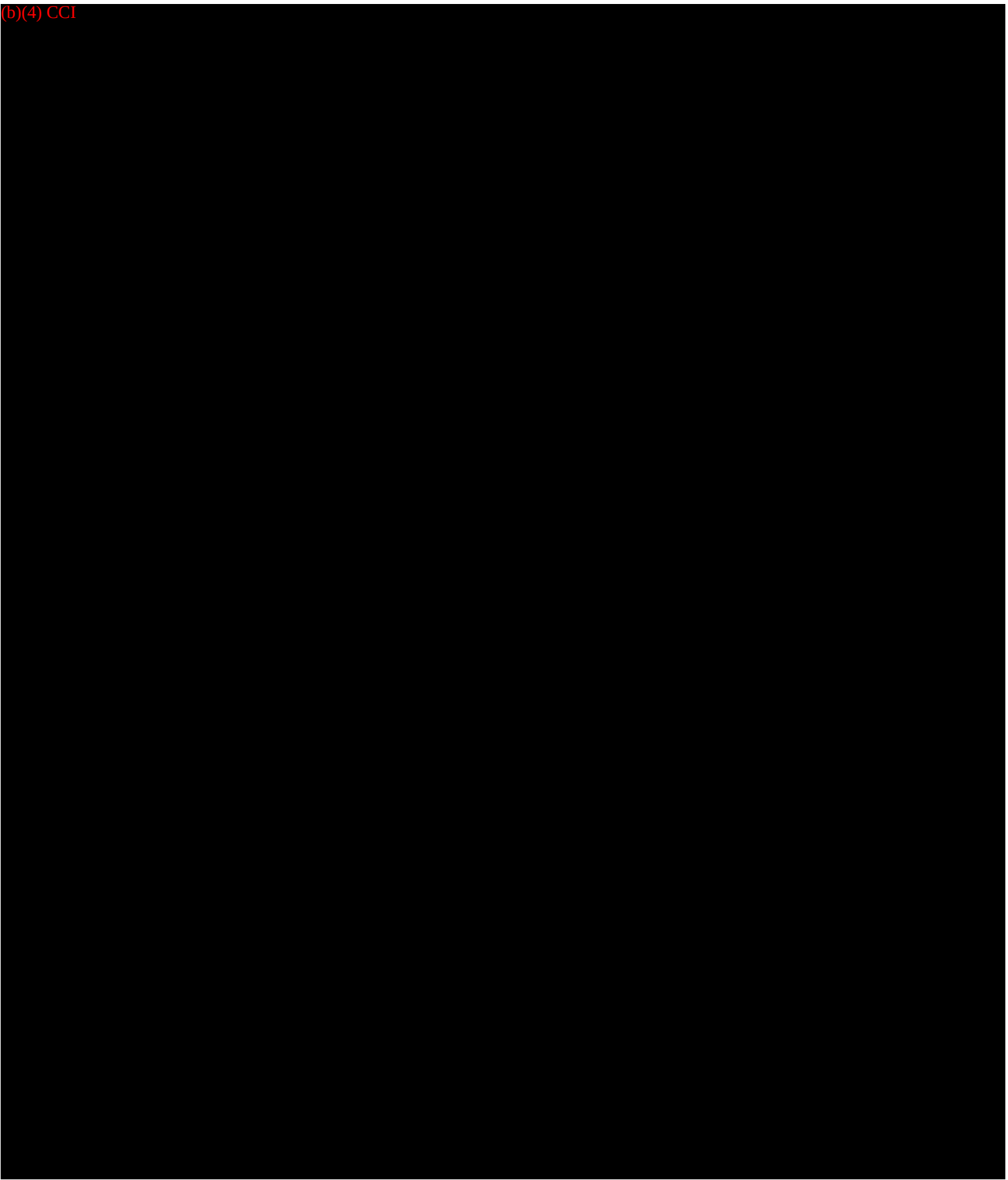
See **Attachment Q12-3** for revised OvuSense labeling.

(b)(4)

(b)(4) CCI

MECHANICAL DETAILS

(b)(4) CCI



(b)(4) CCI

(b)(4) CCI

MATERIAL SAFETY DATA SHEET

(b)(4) CCI

[redacted]

(b)(4) CCI

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(b)(4) Study Protocol

(b)(4) Test Report

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(b)(4) Study Protocol

(b)(4) Study Protocol

ATTACHMENT Q3-2

(b)(4) RISK ASSESSMENT

(b)(4) Risk Analysis

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ATTACHMENT Q7-1
OVUSENSE USER MANUAL

(b)(4) Old version User Manual

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ATTACHMENT Q8-1
DUOFERTILITY PREDICATE DEVICE INFORMATION

DEC 2 0 2011

K 102499

510(K) Summary

Submitter Information

Submitter's Name:	Cambridge Temperature Concepts Ltd
Address:	23 Cambridge Science Park
	Milton Road, Cambridge, CB4 0EY
	United Kingdom
Tel:	+44 1223 437 006
Fax:	+44 1223 437 008
US contact:	Scott R. Mackie (Founder Director (USA))
	Cambridge Temperature Concepts
	P.O. Box 390930, Cambridge, MA 02139
Tel:	+1 617 803 1026
Email:	scott@temperatureconcepts.com

Date summary prepared: 13th December 2011

Device information

Trade name:	DuoFertility
Common name:	Computerized Basal Body Temperature Thermometer
Classification name:	Device, fertility diagnostic, proceptive
Product Code:	LHD

Predicate devices

K021978 Nishitomo Co., Ltd. Petit Sophia

K050094 Lady-Comp USA. Lady-Comp

K033534 Mini-Mitter Co., Inc. VitalSense

Description of device

The DuoFertility system is a computerized basal body temperature thermometer with the following features:

1. A temperature Sensor with integrated data logger to monitor temperature throughout sleep and store the temperature readings
2. Measuring accuracy within +/- 0.05 deg C
3. Adhesive patches to hold the temperature Sensor against the users skin
4. Radiofrequency communications hardware to transmit the stored temperature data to a receiving device
5. Microprocessor based Reader to process and display temperature readings and fertility information.

Indication for Use

The DuoFertility Monitor is intended for measuring, and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Predicate Device Comparison

DuoFertility is a Proceptive Diagnostic Fertility Device (Product Code LHD) so the primary predicate device is the Petit Sophia Fertility Monitor (K021978).

A second predicate device, the Lady-Comp computerized basal body temperature thermometer K050094), is also included as comparative clinical testing has been conducted with this device

The Indications for Use Statement of the DuoFertility Monitor is the same as the Petit Sophia and Lady-Comp predicate devices.

In all of the following key features of a fertility monitor, the DuoFertility Monitor is substantially equivalent to the Petit Sophia and Lady-Comp devices:

- Operating Principle - all devices use the Basal Body Temperature Method
- Temperature Sensor - all devices use a thermistor sensor
- Sensor Accuracy – all devices have an accuracy of +/- 0.05 degrees Centigrade
- User Inputs – all devices have the facility for user input of relevant data
- PC Display - both the DuoFertility Monitor and Petit Sophia devices have the facility for display of temperature graphs plus additional information on a computer.

The following are the new technological characteristics of the DuoFertility Monitor with respect to the Petit Sophia and Lady-Comp fertility monitors.

- Number of Sensors - The Petit Sophia and Lady-Comp fertility monitors use a single thermistor temperature Sensor whereas the DuoFertility Monitor uses 2 thermistors plus an accelerometer/movement Sensor. The additional Sensors do not raise any safety issues and are incorporated to improve effectiveness.
- Number of Measurements - The Petit Sophia and Lady-Comp fertility monitors record a single temperature measurement taken by the user soon after waking up whereas the DuoFertility Sensor logs measurements periodically, forming a time-series of movement, temperature and heat-flow data. These reduce many sources of systematic and random error and are utilised to improve effectiveness..
- Body worn Sensor - Body worn Sensor - The Petit Sophia and Lady-Comp monitors are only used for five minutes on waking up whereas the DuoFertility Sensor is attached to the body for extended periods (at least during periods of sleep). The benefit of the body worn sensor is that data is collected automatically with no need to perform a five minute temperature measurement immediately on waking. Automatic measurement reduces potential human error from the temperature measurement process.
- Location of Temperature Measurement - The Petit Sophia and Lady-Comp fertility monitors utilize oral temperature measurement whereas the DuoFertility Monitor utilizes axillary temperature measurement. Both oral and axillary are well established locations for body temperature measurement.

However DuoFertility has one additional technological characteristic, wireless communication of data from skin temperature Sensor, so a tertiary predicate device, the VitalSense Physiological Data Logging Device (K033534) is considered with regard to this characteristic.

The VitalSense Sensor continuously transmits the data to the data logger which must be within the 2 meter operating range whereas the DuoFertility Sensor only transmits the data when the user selects to do this by placing the Sensor on the Reader. Both the DuoFertility and VitalSense systems use wireless communication for transmission of temperature data from a skin sensor. The differences in the two transmission methods relate to specific features for the different applications. The DuoFertility Monitor has particular advantages for the fertility monitor application. The differences in the technological characteristics of the Sensor data communication do not raise any issues of safety or effectiveness.

The DuoFertility Monitor has identical Indications for Use Statement as the Petit Sophia and Lady-Comp devices and the new technological characteristics do not raise any issues of safety and effectiveness. It is therefore concluded that the DuoFertility Monitor is substantially equivalent to the existing marketed predicate devices.

Non-clinical tests

Cambridge Temperature Concepts has conducted the following non-clinical tests:

- Temperature measurement
  - 5 factory-calibrated Sensors were tested to determine the accuracy, precision and drift characteristics of Sensors for the DuoFertility system.
  - The test protocol comprised the following:

        - Expose to known temperatures, by immersion in a calibrated, computer-controlled waterbath, over the expected range of human body temperatures.
        - Expose to a known temperature at approximately human body temperature by immersion in a calibrated waterbath, to monitor drift over at least 24 hours.
    - The results demonstrate that the tested Sensors were within the required specification of ±0.05 degrees C for each of accuracy, drift and precision over a 24-hour period.

- Electro-magnetic compatibility
    - All EMC testing was conducted by an independent Test House
    - The DuoFertility System passed all applicable EMC emissions and immunity tests required by EN 60601-1-2:2002 (IEC 60601-1-2:2001) and the FCC requirements defined in 47 CFR 15.

- Electrical safety
    - The conformity assessment was conducted by an independent Test House
    - Assessment was conducted in accordance with EN 60601-1:1990 + Amendments Medical electrical equipment - Part 1: General requirements for safety (IEC 60601-1:1988 + Amendments)
    - All safety tests passed (2 labeling issues corrected)

- Biocompatibility testing
    - The sensor and adhesives were tested by an accredited laboratory for cytotoxicity, maximization sensitization and primary skin irritation in accordance with the ISO 10993 family of standards including.
    - All tests showed the DuoFertility sensor and adhesive materials to be safe for use in the intended manner.

- Software
    - Software verification testing has demonstrated that the sensor, reader, PC and server software comply with the requirements of the Software Requirements Specification.

Clinical tests

Cambridge Temperature Concepts enrolled subjects in a clinical study to collect data comparing temperature readings measured with DuoFertility compared to the Lady-Comp predicate device. Subjects included women who were not familiar with the device and relied on instructions provided in the device labelling. Analysis of data from 21 menstrual cycles demonstrated that the DuoFertility monitor is at least equivalent in performance to the Lady-Comp predicate device for the purpose of identifying the date of ovulation. The study also provided evidence that users are able to follow the instructions and use the device as intended.

Conclusion regarding safety and effectiveness

Comparison of the intended use and technological characteristics with the predicate devices and the results of non-clinical and clinical tests demonstrate that the DuoFertility system is substantially equivalent to the predicate devices.

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

Mr. Scott Mackie
Founder Director
Cambridge Temperature Concepts Ltd.
P.O. Box 390930
CAMBRIDGE MA 02139

DEC 2 0 2011

Re: K102499
Trade/Device Name: DuoFertility
Regulation Number: None
Regulation Name: None
Regulatory Class: Unclassified
Product Code: LHD
Dated: December 7, 2011
Received: December 13, 2011

Dear Mr. Mackie:

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,

Herbert P. Lerner, M.D., Director (Acting)
Division of Reproductive, Gastro-Renal
and Urological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number: K102499

Device Name: DuoFertility

Indications for Use:

The DuoFertility Monitor is intended for measuring, and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ (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)

(Division Sign-Off)
Division of Reproductive, Gastro-Renal, and Urological Devices
510(k) Number K102499

DuoFertility
Advanced Fertility Monitor

Quick Start Guide & User Manual

The help and support you need to get pregnant - naturally

A message from the team

Thank you for choosing to use DuoFertility to help you conceive. Please read this guide carefully before using the product.

We are committed to making this journey as natural and simple as possible for you. The DuoFertility system provides you with an easy way of keeping track of your body basal temperature, which is a clinically proven method of monitoring your fertility. DuoFertility uses the latest technology to identify the days in the month you are most likely to get pregnant with an accuracy of 99%. It has been designed to fit into any lifestyle, so you should be able to use the product without any disruption to your daily life.

If you would like further advice on how to use DuoFertility, please do let us know. Our customer care team are happy to answer any queries that you may have about using the product, and our in-house team of dedicated fertility experts are available to answer any fertility-related queries that you may have. Any technical terms are explained in the Glossary (Pages 29-30).

We hope that you enjoy using DuoFertility, and that it helps you to take control of your fertility.

Best wishes from the team at
DuoFertility

Contents

General product information

A step-by-step guide to using DuoFertility

Additional information

Quick Start Guide

Basic functions

To switch ON the reader, hold the central button for 3 seconds. The DuoFertility logo will flash white.

The reader turns itself OFF automatically; after about a minute, the DuoFertility logo will stop flashing, indicating that the reader is off.

Getting started

Please start using your DuoFertility product as soon as you receive it:

1. Turn on your reader by pressing the central button.
2. Press the central button of the reader a second time. You should see a yellow light moving backwards and forwards on the light scale.
3. Place the sensor on the central button. A green light should appear on the left hand side of the light scale and will move slowly to the right hand side.
4. Once the transfer is finished, you should hear a low beep followed by a high beep, and the green 'today' arrow should light up in green. Note that the transfer may take up to half an hour the first time that it occurs, so we recommend that you leave the sensor on the central button and do something else while it downloads.

This process will read out the temperature data that it has been logging while in transit. Once this is done, you can start wearing the sensor to collect your personal temperature data.

5. Use one of the adhesives in the testpack provided to start wearing the sensor under one of your arms. Make sure that you position the sensor so the side with the large, blue central circle is facing your skin. Remember to wear the sensor while you are sleeping.
6. After a couple of days, transfer the data from the sensor to your reader by following Steps 1-4 above. This time, the data should be quicker to download, and so there is no need to remove the sensor to perform the download. You can hold the reader up to the sensor instead, as demonstrated in the instructional video:
   http://www.duofertility.com/duofertility/product-video-demos

After you have been using DuoFertility for approximately one cycle, your fertility status should start to be displayed on the reader light scale after the download. It is important for you to read the rest of the User Manual to learn about how to use the product in greater detail.

Contents of the DuoFertility box

The DuoFertility box should contain:

1. The DuoFertility reader
2. The DuoFertility sensor
3. Testpack of adhesives
4. A USB cable
5. Quick Start Guide & User Manual
6. Adhesive User Manual
7. HCG Manual
8. A small travel bag
9. 5 pregnancy tests

If any of these are missing, please call the DuoFertility careline.

How DuoFertility can help you

DuoFertility is a sophisticated fertility monitor. It predicts when you are most likely to be fertile by automatically taking continuous measurements of your temperature. This allows the technology behind DuoFertility to build up a detailed picture of your cycle and predict your most fertile days with an accuracy of up to 99%. After transferring this data from your sensor, your reader will display a simple summary of your fertility status which you can use to plan intercourse for the best time of the month.

DuoFertility maximises your chances of getting pregnant by helping you to:

- Plan intercourse for when you are most likely to conceive
- Understand your fertility by viewing a detailed picture of your menstrual cycles

How DuoFertility works

DuoFertility consists of a sensor and a discreet, hand-held reader. The sensor continuously takes 20,000 measurements of your temperature every 24 hours. This allows it to detect the small jump in temperature which occurs when you ovulate, and to identify when you will be most likely to conceive, giving you time to plan a romantic evening.

When ovulation occurs, there is a small increase in your body basal temperature (see Figure 1). (Body basal temperature is the lowest temperature your body reaches – your body usually reaches this temperature during deep sleep and your temperature increases again when you wake up.) The change in body basal temperature before and after ovulation usually ranges from 0.3°C to 1.5°C, although this may vary.

The technology behind DuoFertility records skin temperature measurements and uses this to estimate your body basal temperature; this allows it to identify the small rise in body basal temperature and to confirm that you have ovulated. DuoFertility works out when you are sleeping most deeply, so there are no disruptions to your temperature measurements from late nights, early mornings, or interrupted sleep. Of the 20,000 temperature points collected, only the best quality measurements are used.

The most fertile days of the menstrual cycle usually include the day of ovulation and the days preceding and following ovulation. Therefore, accurately identifying your ovulation allows the technology behind DuoFertility to pinpoint your most fertile days with an accuracy of 99%, helping you to plan intercourse for when you are most likely to conceive.

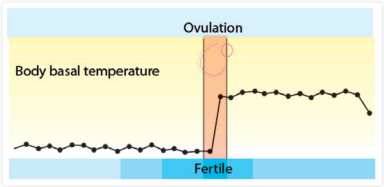


Figure 1: Variations in body basal temperature during the cycle (each dot represents BBT at a given day of the cycle). There is a small increase in BBT on the day of ovulation.

Getting the most out of DuoFertility

There are a number of things you can do to get the most out of DuoFertility and maximise your chances of getting pregnant:

Regularly plug the reader into a computer with an Internet connection

While it is possible to check your fertility status and enter in fertility clues using just your reader, we strongly recommend that you regularly plug your reader into your computer and open your temperature chart while you are connected to the internet. This is because we regularly release automatic updates to ensure that DuoFertility becomes more attuned to your body as time goes on, helping to maximise your chances of getting pregnant. Regularly plugging in your reader will also allow us to detect any problems with your product by checking for irregularities in your data and monitoring the battery voltage of your sensor. In addition, all of your data will be encrypted and saved so that none of your data will be lost if you happen to lose your reader. For further information, please read Page 19.

We suggest that you keep your reader plugged into your computer for at least half an hour every week. It is particularly important to log in more regularly early on in your cycle.

Record each day of your menstruation on the day that it occurs

In order to ensure that the fertility predictions that you receive are as accurate as possible, we strongly recommend that you record each day that you have your period either on the reader or on the software. It is very important that you record menstruation as soon as possible after it occurs - ideally, you should record each day of menstruation on the day that it occurs, or, at the very latest, within 2 to 3 days of it occurring.

Inform us of your fertility history

It is very important for you to respond to the email sent from our fertility experts with full details of your fertility history so that we can personalise your product. It is particularly important for you to email us your previous cycle dates from before you started using DuoFertility. This will enable your fertility predictions to be adjusted to the regularity and length of your cycles so that they are as accurate as possible. We also suggest that you keep us updated about any changes in treatment or medication that you undergo while you are using DuoFertility.

Understanding your menstrual cycle and ovulation

The menstrual cycle is the process during which your body prepares for pregnancy. As you approach ovulation each month, your uterus becomes more welcoming to sperm, allowing them to survive longer and swim to the egg, which increases your chances of getting pregnant.

Each menstrual cycle begins on the first day of your period and ends on the day before your next period. The menstrual cycle is composed of three different phases and lasts 28 days on average, in which case ovulation is expected to occur between day 11 and day 16. However, it is not unusual to have cycles which are as short as 24 days or as long as 60 days.

Ovulation is a key event in the menstrual cycle. During the follicular phase, one of the follicles which are contained by the ovaries reaches complete maturity and one egg/ovule is released. This is triggered by a surge in luteinising hormone (LH).

After ovulation, the released egg travels along the Fallopian tubes, where fertilisation by sperm can occur. The ruptured follicle left behind after ovulation forms the corpus luteum which secretes progesterone, the hormone responsible for the rise in body basal temperature (BBT) that signals ovulation. It also suppresses the ripening of further follicles, induces closing of the cervix and the thickening of cervical mucus. The corpus luteum then disappears with the onset of menstruation.

The lifespan of the released egg is only 24-48 hours. Therefore, for fertilisation to occur, sperm must either be already present in the female reproductive tract, or intercourse must take place soon after ovulation. Sperm can survive for 3 to 5 days in the vaginal environment if the right kind of cervical mucus is present. This is why the few days before and after ovulation are when you are most likely to get pregnant, with the peak time being the day of ovulation.

When you ovulate, the vaginal environment becomes more welcoming and friendly to sperm, making this the most fertile time of your cycle and therefore the best time to try for a baby. Cervical mucus becomes less acidic and more elastic and the cervix moves from a low, firm, dry and closed position to being soft, high and open. All these changes facilitate the passage of sperm to the uterus and the Fallopian tubes. This is therefore the best time of the month to try for a baby.

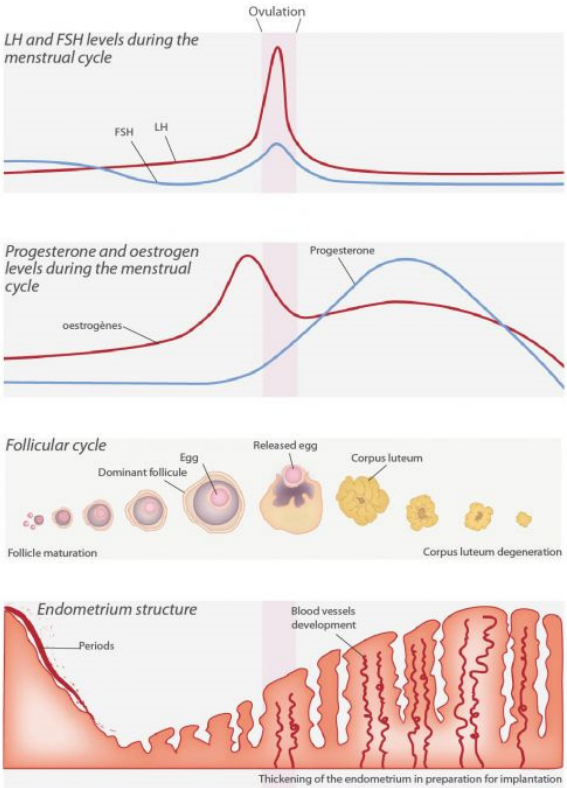


Figure 2: Phases of the menstrual cycle

Limitations of use

DuoFertility should not be used as a contraceptive device. DuoFertility was designed as a fertility monitor and should not be used for any other purpose. If you wish to learn more about natural family planning, you should see a natural family planning expert who will be able to help you identify your natural cycle.

DuoFertility is suitable for women with a wide range of conditions, such as hormonal disorders (including polycystic ovarian syndrome) and irregular menstrual cycles. It is also suitable for women who are currently undergoing, or have undergone, assisted reproductive techniques such as IVF or ovulation induction.

Certain medical conditions and medications can adversely affect the performance of DuoFertility. DuoFertility will not be able to help women who are suffering from anovulation because of menopause, have both Fallopian tubes blocked, or whose partner is unable to produce any sperm (azoospermia).

Please speak to your doctor, or contact our careline on +44 1223 437 003, if you need further advice.

How to use the sensor

Where to place the sensor

The sensor must be worn in an area with good blood circulation. We suggest using the adhesives which are provided to keep the sensor in place under the arm, as this is a convenient place to wear the sensor. If for some reason this position does not suit you, please contact us and we will help you choose a suitable alternative.

You can wear the adhesive either underneath or away from your bra strap. This should not affect the results as long as you are consistent in where you position the sensor. You should try to find the position that is most comfortable for you. After you have removed the sensor, please try to replace the sensor in the same position in which you were previously wearing it.

Unless you have reached the beginning of a new cycle (i.e. your period has started), we do not recommend that you change the arm under which you are wearing the sensor. This is because the blood flow might be slightly different in each arm, and this could affect the quality of the temperature readings. If, for any reason, you have to change arm, we suggest that you record this directly onto your PC software. The correct time to change arm is on the first day of your period, as this marks the beginning of a new cycle. This allows the skin on each arm to breathe for a month, and will also reduce the chances of any skin irritation.

How to apply the sensor

It is very important for you to wear the sensor the right way round, otherwise it will not be able to take accurate measurements of your temperature.

The side of the sensor that goes next to your skin has a large blue central circle (Figure 1). The outward side of the sensor has four smaller circles (Figure 2). Position the sensor so that the skin side is facing down.

Figure 1: Skin side of the sensor

Figure 2: Outward side of the sensor

When to wear the sensor

We recommend that you wear the sensor continuously - this ensures that the maximum number of readings is taken, resulting in greater accuracy. One of the advantages of DuoFertility is that you do not have to wake up early every day to take your temperature - the sensor does all the work for you.

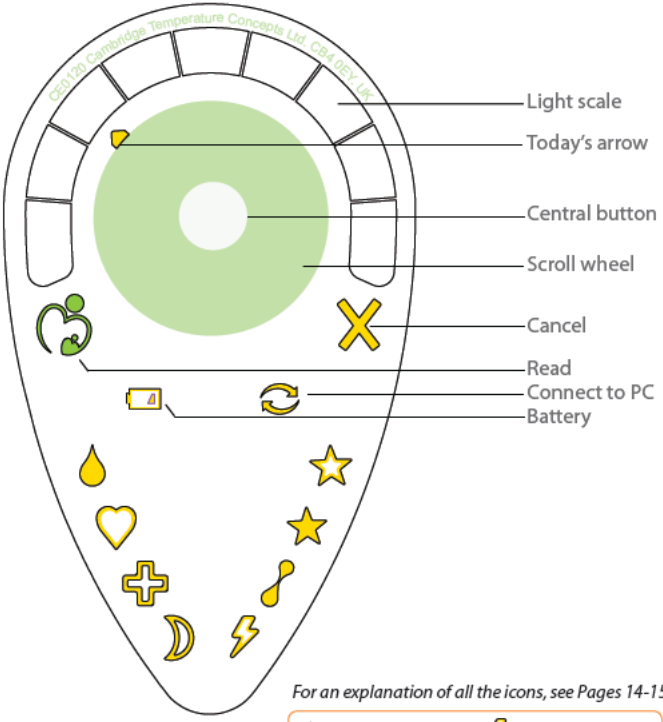
The sensor is fully waterproof, so you can wear it in the shower or in the swimming pool. It can also be worn during intense exercise in the gym. Occasionally, however, you may not want to wear the sensor, for example,when wearing a bikini. If you remove the sensor during the day, it is very important that you remember to put it back on when you go to bed so that data is collected every night.

We understand that everyone's skin is different so if you have sensitive skin, please refer to Page 8 of the Adhesive User Manual or contact the customer careline.

How to change the adhesive

After removing the adhesive, we recommend that you leave the sensor off for a few hours, making sure that you replace it before you go to sleep. This allows your skin to breathe and reduces the risk of skin irritation. Please see the Adhesive User Manual provided for full instructions on how to change the adhesive.

The reader



For an explanation of all the icons, see Pages 14-15.

Period	Ovulation pain
Intercourse	Cervical mucus
Feeling ill	Star 1
Disrupted sleep	Star 2

How to use the reader

You can interact with the reader by using the scroll wheel and the central button. The different icons which appear along the edge of the reader indicate the different functions that are available, and the light scale is used to display your fertility status. In order to find out how to read your fertility status on the reader, please turn to Page 21.

How to switch the reader ON and OFF

To switch the reader on, hold the central button for 3 seconds. The read icon will flash white, indicating that the reader is ready to be used.

You cannot switch the reader off manually - the reader will turn itself off automatically after about a minute. When the read icon stops flashing, this indicates that the reader has turned itself off automatically; you will have to switch it back on in order to use it.

How to select an icon

To select an icon on the reader, start by running your finger anti-clockwise around the scroll wheel and the icons will light up one by one, in white. When an icon is lit in solid white, you can select it by pressing the central button. The icon will then flash to indicate that it is waiting for you to enter further information. The reader will beep each time an icon is selected.

After you have entered information into your reader, that icon will light up in pink as you continue to scroll through the other icons on the reader. If you scroll back to that icon, the reader light scale will automatically display the information that you entered for that icon. If you wish, you can edit this information and correct any mistakes that you made.

When the reader turns itself off automatically, this marks the end of a session; when you turn your reader back on again, the icons that you previously entered will no longer show up in pink, and that data can only be edited by running the software.

How to cancel an icon

To cancel a piece of information that you have entered onto the reader, please follow the steps below:

1. Select the 'cancel' icon. It will light up in white.
2. All of the icons entered during that session will light up in pink. Use your scroll wheel to move to the icon you want to cancel and press the central button.
3. The icon will turn red to indicate that it has been cancelled.

Entering information onto the reader

You can use the icons which appear on the reader to enter in further information to help DuoFertility to refine its prediction of your fertility. For information on the meaning of each icon, please turn to Pages 14-15.

All of the icons on the reader, apart from intercourse, ovulation pain and star 1, require you to specify a quantity. For example, if you select the illness icon, you can use the reader to enter in exactly how unwell you are feeling.

Entering period, illness, sleep disruption, cervical mucus and star 2 icon information on the reader

1. Use the scroll wheel to select the icon corresponding to the data that you want to enter and press the central button. The icon will flash in white.
2. Use your finger to scroll clockwise on the scroll wheel. This will light up a different number of segments on the light scale, depending on the amount you would like to specify. Please note that the light scale will light up in a different colour, depending on which icon is selected (see Page 15).
3. When you have selected the appropriate number of segments, press the central button to store the data.

For example, in the case of illness, if you are only feeling slightly unwell, you can turn the scroll wheel so only a few sections on the light scale are lit. If you are feeling very unwell, you can use the scroll wheel to select a high number of sections.

Entering intercourse, ovulation pain and star 1 information on the reader

1. Use the scroll wheel to select the icon corresponding to the data that you want to enter and press the central button. The entire light scale will light up.
2. Press the central button. The icon will flash white, indicating that this information has been saved.

Reader icons

The DuoFertility reader can identify when you are most fertile solely by using the temperature data which is recorded by the sensor. However, there are a number of additional pieces of information which you can enter to increase the accuracy of prediction. We highly recommend that you enter the "essential icons" listed below to improve the accuracy of prediction. The "additional icons" are not essential for you to enter; however, any extra information may be helpful in refining the identification of your fertile window.

Essential icons

"Read" icon

The "read" icon will flash white when the reader is turned on. The icon will start to flash yellow once data transfer from the sensor has started .

"Intercourse" icon

You should use this icon to enter in each time that you have intercourse. It is a simple yes/no answer; press the central button and the icon will flash white, indicating that this information has been saved, and the entire light scale will be lit in pink.

"Period" icon

You should use this icon to enter in the level of menstrual flow on each day of your period. Use the scroll wheel to enter in the level of flow by pressing the central button when the correct amount of red light appears on the light scale. This can help to differentiate between spotting and periods and will indicate the end/beginning of each new cycle.

"Cancel" icon

When you select the "cancel" icon, you can then scroll between the icons that have been entered in the current session, and the light scale will display the information that you entered for each icon. Use the scroll wheel to select the icon which you would like to cancel and press the central button. That icon will then light up in red, indicating that this information has been cancelled.

You will only be able to select the "cancel" icon if you have entered information onto the reader during the current session.

"Battery" icon

If the reader needs recharging (the battery will flash red), plug the reader into the USB port of a computer that is turned on. The battery icon should turn solid yellow and the battery will start recharging immediately. When the battery is fully charged, the battery light will turn solid green; you can then unplug the reader. Unlike mobile phones, the number of bars in the battery icon does not increase as the reader is charged; the icon simply changes colour. Make sure that you unplug your reader from your computer when your computer is off.

"Connect to PC" icon

When the reader is plugged into a computer, this icon will normally turn green. If an error occurs, the icon will flash blue. In this case, please plug the reader into a computer and run the software. When the software is running, this icon will turn solid blue. If the flashing blue continues, contact the DuoFertility careline

Additional icons

"Illness" icon

If you are feeling unwell, select this icon. Use the scroll wheel to rate how unwell you are feeling and press the central button when the correct amount of green light is displayed. Illness may affect your temperature.

"Disrupted sleep" icon

If your sleep has been disturbed, you should select this icon. Use the scroll wheel to rate the level of sleep disruption and press the central button when the correct amount of dark blue light is displayed.

"Cervical mucus" icon

The quantity of cervical mucus varies during each cycle. Use the scroll wheel to rate the quantity of your cervical mucus and press the central button when the correct amount of yellow light is displayed.

"Ovulation pain" icon

If you experience ovulation pain, select this icon. It is a simple yes/no answer; once you have selected this icon, the light scale will be lit in yellow and the icon will flash white, indicating that this information is saved.

"Star" icons

The star icons can be used to enter additional user-defined fertility clues such as libido, breast tenderness and ovulation tests.

How to use the software

If you have Windows 2000/XP/Vista or MacOS 10.4 or higher, you can plug the reader into your computer to see an overview of your cycle, as well as modify or add any further information. It is very important for you to plug your reader into your computer and run the software at least once a week.

Plugging the reader into a computer allows you to:

- View the changes in your temperature plotted on a graph since you have started using the product
- View all the information which you have entered into the reader
- Enter in notes for different days
- Add information retrospectively

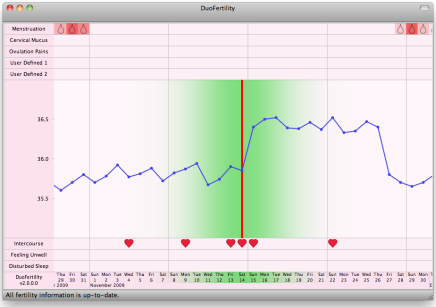
Using the software

Before you start using the software, you must make sure that the clock on your computer is set to the timezone that you want to use on an ongoing basis i.e. it should not be set to a holiday timezone.

Next, connect the reader to one of the USB ports on your computer using the cable provided. The reader will appear as a removable drive containing a file called "Info" which links to the DuoFertility support site where you can download the latest software.

A progress bar will appear on your screen (see above) while the software is being loaded and a blue light will appear on your reader light scale. Once this is finished, a window will appear which will display your temperature chart up to the last day on which you transferred your data. Temperature is displayed along the vertical axis, and dates are displayed along the horizontal axis. The rows at the top and bottom of the chart represent all the information you have entered into the reader e.g. period, intercourse etc. You will be able to see and change any information which you entered previously, and enter information retrospectively.

You can scroll backwards on your chart to view data for past dates by clicking on the graph and dragging it. Alternatively, you can use your mouse wheel. You are not able to scroll more than one week into the future. When you hover over a column, the date which your mouse is hovering over will turn bold.

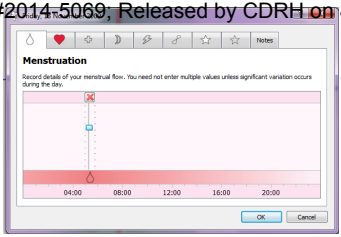


Entering information into the software

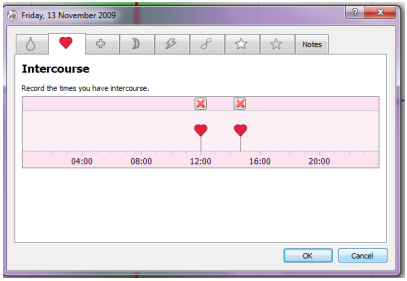
You can use the software to enter in all the information that you enter into the reader, as well as writing notes. We suggest that you refer to Pages 14-15 to familiarise yourself with the meaning of each icon. In order to enter information, please follow the steps below:

1. Position your mouse on the chart so that it is above the correct date. This date should be highlighted in bold at the bottom of the graph. Double-click your mouse.
2. A window will appear with nine tabs allowing you to enter in period, intercourse, illness, sleep disruption, ovulation pain, cervical mucus, star information and notes. Please click on the tab which displays the icon that you would like to enter information for.
3. A window will appear with a range of times displayed along the bottom.

If you are entering in **information which requires you to specify a quantity**, such as menstruation, you should click in the box above the relevant time*. An icon will appear above that time with a slider which you can drag up or down to adjust the amount of menstrual flow you have had. If you would like to cancel your entry, simply click on the cross which appears above the entries.



If you are entering in **information which requires a simple yes/no answer**, such as intercourse, you should click in the box above the relevant time. An icon will appear above that time. If you would like to cancel your entry, simply click on the cross which appears above the icon in the box.



Once you have entered in the information, click "OK" to save your changes. The relevant icon should now appear on your chart.

*Please note that you do not always have to specify the exact time when entering in some pieces of information. For example, with icons which require you to enter in a quantity, such as period, illness and cervical mucus, it is not necessary to specify an exact time. However, with icons which require a yes/no answer, entering in a time is more important.

Entries appear at the point in time they are made on the reader.

You only need to enter multiple values in one day if a significant change has occurred.

Leaving notes on the software

The DuoFertility software allows you to write notes for each day. These notes could include details of changes in your medication, any changes in your lifestyle or new treatments that you are undertaking. All of these details will be taken into account when your fertility prediction is calculated.

To do this, simply follow Steps 1 to 2 in the "Adding Information" section, and select the tab entitled "Notes". Enter in the relevant details in the text box and click "OK" to save your changes. An icon will appear in your chart to indicate that a note has been written for that day.

Transferring your data to the DuoFertility servers

When you plug your reader into a computer with an Internet connection and open your temperature chart, your data will automatically be transferred to our servers. This will ensure that you receive the latest updates, and will allow us to monitor the performance of your product.

A message will appear at the bottom of your chart to indicate how much of your data is being transferred. Once all of your data has been successfully transferred, you will see a message saying "Synchronisation Complete" at the bottom of your chart. You will also see messages at the bottom of your chart when you a software or firmware update is being carried out. If your data fails to transfer to our server, you will see a message saying "Attempting to connect". In this case, please check that your computer is connected to the Internet. If your data still fails to be transferred, please contact our customer careline.

Transferring data from the sensor

Your temperature data is recorded and stored on the sensor, but you will need to transfer this information to the reader before you can view your fertility status.

How do I transfer the data?

In order to transfer your data, please perform the following steps:

1. Turn on the reader by pressing the central button once.
2. Press the central button a second time. A yellow light will move across the reader's light display from left to right, indicating that the reader is looking for the sensor. The reader is now ready for the download to take place.
3. Hold the reader up to where you are wearing the sensor, so that the sensor is resting against the reader's central button. This will start the data transfer.

4. Continue to hold the reader in place against the sensor. During the transfer, the "read" icon will flash yellow, and a green light will move more slowly across the light display from left to right; the transfer is not complete until the light has moved all the way across the display. Once the transfer is complete, the reader will make a beep, low then high. (If your reader makes a different beep, high then low, the download has not been successful - please see Page 23 for further details.)
5. Look at the light scale on the reader. The arrow on the reader which indicates today should be lit up in green and your fertility status should be displayed.

A full demonstration is available on the DuoFertility instructional video which can be found at http://www.duofertility.com/duofertility/product-video-demos.

IMPORTANT

If you find it too difficult to download your data while wearing your sensor, we suggest that you remove the sensor before carrying out the transfer. You should also do this the **first time that you transfer data from your sensor to the reader,** since the initial transfer may take up to half an hour to perform. We recommend that you follow Steps 1 to 2 above, then remove the sensor and place it on the reader so that it is resting against the central button. You should then continue with Steps 4 to 5 as outlined above.

Your **fertility status will only be displayed once the data transfer has been fully completed** i.e. after the reader makes a low beep followed by a high beep. You will not be able to view your fertility status if you remove the sensor before this.

How long does it take to transfer the data?

The data transfer usually takes up to 90 seconds per day of data. However, please bear in mind that, if you have just received a new sensor, it may take a total of up to 30 minutes to transfer the data recorded during shipment. If the data transfer is occurring very slowly, it is fine for you to leave the sensor on the reader while you continue doing something else.

How often should I transfer the data?

You can transfer your data whenever it is most convenient for you; there is no need to transfer your data every day. However, during the first few months of usage, we recommend that you transfer your data every couple of days. Please also bear in mind that the less frequently you transfer your data, the longer the data transfer will take.

Reading your fertility status

Once you have transferred your data to the reader, you should be able to see an indication of your fertility status. You can read the results either directly from the reader or from your PC if you wish to view a more detailed display of your fertility status.

Please bear in mind that the DuoFertility reader needs at least one full cycle of temperature data before it can display your fertility status.

Displaying your fertility status on the reader

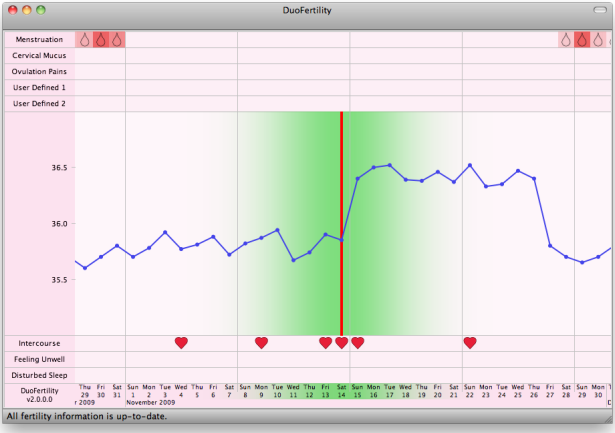
If you are approaching your fertile days, your fertility status will automatically be displayed after you have transferred data from your sensor. If you wish to view your fertility status but do not have your sensor with you, you can still view your fertility status on your reader provided that you have carried out a sensor download and viewed your fertility status within the last 24 hours. You can do this by turning on your reader and pressing the central button. The yellow light will move back and forth on the light scale, but given that there is no sensor present, no download will occur - instead, your fertility status will be displayed on the light scale.

Your fertility status for the previous two days and the next six days will be displayed on the light scale of the reader. The intensity of each day represents differing levels of fertility. A weak light indicates that you are unlikely to be fertile that day, whereas a strong light indicates a fertile day.

The black triangle next to the scale always shows the data for 'today'. This shows that your fertile window is approaching, with ovulation predicted for 3 days time (the darkest shade of green) and the three most fertile days on and around this day. This indicates that you are in your fertile period.

Displaying your fertility status on a computer

You can plug your reader into a computer to view your fertility status in greater detail. The software indicates which days you are most fertile by the green shading which appears. If there is no shading, this indicates that this is not the most fertile time of your cycle. Faint green shading suggests that your fertility status on that particular day is low, and strong green shading indicates that you are at the most fertile of the month and that this is the best time to try for a baby. As you can see from the graph, there is only a small chance of conceiving until up to 6 days before ovulation and up to 4 days after, although this may vary very much from couple to couple.



A red line will appear on your chart up to one week after ovulation has occurred to confirm your ovulation date.

Troubleshooting

DuoFertility has been designed to be intuitive and easy to use, but as with any product, technical issues may occur from time to time. We have therefore included below an easy, step-by-step approach to solving any problems that may arise. If you would like further assistance, or if you are experiencing an issue which is not listed below, please call our careline.

The "Connect to PC" icon on the reader is flashing blue.

This is probably due to the fact that your reader battery has fallen to a very low level and the internal clock on the reader needs to be reset. In this situation, you will not be able to download from your sensor or enter any data. You will also hear a high beep followed by a low beep which indicates that there is a problem with the reader. This can be easily solved by performing the following steps:

1. Plug the reader into your computer. The "Connect to PC" icon should now be flashing green and blue
2. Check that you are connected to the Internet
3. Open up your temperature chart
4. Leave the chart open for a couple of minutes
5. Close down the temperature chart
6. The "Connect to PC" icon should now be solid green. You should be able to use the reader without any problems

My reader is not charging when I plug it into my computer.

When your reader is plugged into your computer, the battery icon should light up in yellow to show that the reader is charging. Unlike mobile phones, the number of bars on the battery icon will not increase while the reader is charging - the battery icon will simply turn green once the reader is fully charged.

Looking after the DuoFertility product

Both the DuoFertility reader and sensor are electronic devices like your mobile phone and so you should take good care of them. To ensure that you get the most out of the product, we strongly recommend you follow the guidelines below:

- Keep both the reader and sensor out of the reach of children.
- The reader and the sensor should be kept out of direct sunlight.
- When not in use, the reader and sensor should be stored in a cool, dry place.
- Interference frequency of 100 to 150 kHz will interfere with the data transfer between the sensor and the reader. However, this is only likely to cause a problem if you transfer your data while standing next to a RF transmitter (such as an AM radio mast) which is highly unlikely unless you work with radio equipment.
- The sensor is fully waterproof but the reader is not. You should keep both the reader and the sensor away from sources of heat.
- The sensor must also be kept away from strong magnetic fields (such as MRI scanners in hospitals).

Cleaning the sensor and reader

The sensor must be cleaned with soapy water at least once a month. The sensor can be re-used for the whole of its lifetime (around 6 months). The reader should not be cleaned with water, but with a dry cloth.

What to do if you lose the sensor

If you lose the sensor, you will need to purchase a new one. Contact our team to ensure that you will be able to read the data from the new sensor with your existing reader.

What to do if you lose the reader

If you lose the reader, you will need to purchase a new one. Contact our team to ensure that you will be able to read the data from your existing sensor with your new reader. You should continue to wear your sensor while you are waiting for a replacement reader as the sensor can store up to 1 month of data. Make sure that you also consistently record your fertility clues while you are waiting to receive your new reader. You will be able to enter all the clues onto your computer as soon as you receive your new reader.

If you regularly plug your reader into a computer with an Internet connection and open your temperature chart, DuoFertility will not need to learn about your cycle from scratch when the new reader arrives. It will be able to access all your previous data the first time that it is plugged into your computer.

Frequently asked questions about DuoFertility

When should I start using DuoFertility?

We suggest that you start using DuoFertility as soon as you receive it, rather than waiting until the beginning of your next cycle. This will allow the sensor to collect as much valuable temperature data as possible which will help to ensure the accuracy of all the fertility predictions that you are given.

Do I have to use all the symbols on the reader?

For most people, the correct measurement of BBT is enough to reliably identify the fertile window. Nevertheless, entering in more data will increase the accuracy of detection of your fertile window, especially if your cycles are very irregular.

What should I do if I have stopped using the DuoFertility system for some time?

Please let us know if you are planning to have a break from using DuoFertility. We recommend that you continue to make a note of your menstruation so this can be entered into the reader in the future.

If you have continued to wear the sensor, simply start using the handheld reader again, as the sensor can store up to 1 month of data. If you have not been wearing the sensor, start again whenever you want. You should ideally enter the date of your last period on your computer once you start using DuoFertility again. Bear in mind however, that you may have to wait at least one cycle before getting any results.

How does DuoFertility keep my private data secure?

We ensure that all customer data is kept secure and completely confidential. All data that you upload to our servers is also encrypted.

Can DuoFertility tell me whether I am pregnant?

Some women display temperature patterns in the week following ovulation which are characteristic of pregnancy. These patterns are typically an elevated temperature after the first day of the following cycle (the expected date of your next period) and tend to occur once implantation has taken place. However, this is only an indicative sign and a blood-hormone pregnancy test is the only way to be sure.

Why are the readings on my temperature chart below 37^{0}C?

The DuoFertility sensor takes measurements of your skin temperature and uses this to approximate your body basal temperature. Skin temperature is usually a few degrees lower than core body temperature, which is why the temperature readings on your chart will probably be below 37^{0}C.

Will wearing the sensor set off security at an airport?

Not wearing the sensor will not set off security.

Will using DuoFertility interfere with other electronic devices I am using (such as a pacemaker)?

No, DuoFertility will not interfere with other medical electronic instruments. The only interference that might occur is from an RF transmitter (such as an AM radio mast) which is highly unlikely.

Can I use deodorants or moisturisers when I am wearing the DuoFertility sensor?

Yes, you can, but before sticking the sensor to your skin, you must ensure that your skin is free of all moisturiser and deodorant as this might result in loosening of the sensor. However, once the sensor is stuck onto your skin, you can apply deodorant.

Can I remove the sensor from my skin to transfer the data to the reader?

It is important for the sensor to be very close to the reader to ensure that the transfer of the data is successful. We suggest that you keep the sensor on and hold the reader up to carry out the data transfer in order to conserve your adhesives; however, if this is uncomfortable, we recommend that you remove the sensor from your skin and place it on the central button of the reader. You can then leave the transfer to take place while you get on with something else. We also suggest that you remove your sensor for the data transfer when you are transferring your data for the first time, or if it has been a while since you have transferred your data.

How long do I have to use DuoFertility before it can identify my fertile window?

Since DuoFertility takes several readings a minute, it may be possible to detect the shift in temperature which coincides with ovulation after only several days of use. However, we recommend allowing one cycle for DuoFertility to become accustomed to the way your body works before it can determine the best time to plan baby-making intercourse.

How is a day measured by DuoFertility?

DuoFertility measures one day as being from 6pm to 6pm. Therefore, when you see a temperature point appear on your chart, this displays the temperature which was recorded for the previous night. This also means that you may not see a temperature point appear for a particular day until after 6pm i.e. until after that 'day' is finished.

How do I transfer my data to the DuoFertility servers?

When you plug your reader into a computer with an Internet connection and open your temperature chart, all of your data is automatically transferred to our servers. This allows us to monitor the performance of your product and send you the latest updates. There is no need for you to actively send us your data - the entire process is automatic.

Will travelling in different timezones affect my temperature readings?

No, travelling in different timezones should not affect your temperature readings. However, we recommend that you make a note of the fact that you have been travelling on your software, in case this causes greater variability in your data.

Can I give DuoFertility to a friend to use?

We advise you to only give DuoFertility to a friend to use once you have finished using it yourself. This is because each DuoFertility device is personalised to your cycles. If you would like to pass DuoFertility on to a friend, we suggest that you contact our careline and send your product to our office. We will then be able to remove your data from it and make sure that it is personalised to your friend's cycles.

When will my ovulation line appear on my temperature chart?

The ovulation line typically appears on your temperature chart a couple of days after you have ovulated. However, in some cases, it may take up to a week to appear.

Will sleeping with a hot water bottle affect my temperature measurements?

This should not affect your temperature measurements, unless the hot water bottle is very close to where you are wearing the sensor.

Can I use DuoFertility in the shower? Is it safe?

Yes, the sensor can be worn in the shower or in the swimming pool. But the reader is not waterproof and should be kept away from water.

Can DuoFertility help my doctor diagnose an infertility problem?

In some cases of infertility, information about your cycle can help your doctor to identify a problem. This is why doctors often recommend that you chart your temperature for a few months if you are struggling to conceive. The only difference is that DuoFertility does this automatically for you while you sleep.

Blood test for pregnancy: test a blood test that will confirm whether you are pregnant or not. The hormone measured by this test is Human Chloronic Gonadotropin hCG (a hormone very similar to LH).

Body basal temperature (BBT): the lowest temperature the body reaches while sleeping Particular patterns of BBT can indicate which phase of the menstrual cycle a woman is entering and can therefore be used as an aid to conception. BBT is achieved after at least a couple of hours of deep sleep.

Cervix: the opening between the uterus and the vagina. The position of the cervix changes during the cycle. It is closed, low and firm during the infertile phase, and becomes open, high and soft during the fertile phase.

Corpus luteum: this is formed as the result of the changes occurring to the ovarian follicle following ovulation. Its function is to secrete progesterone which is extremely important for conception as it prepares the lining of the uterus to receive the embryo.

Fallopian tubes: the tubes (ducts) through which the egg travels from the ovaries to the uterus once it is released. The egg is usually fertilised by sperm here.

Fertile window : the phase of the menstrual cycle that is most favourable for conception. It usually begins a few days before ovulation and ends the day after ovulation.

FSH or follicle stimulating hormone: a pituitary hormone which stimulates the development of the ovarian follicles in women and the production of sperm in men.

Hormone: a chemical substance which is produced by an endocrine gland and is then released into the bloodstream.

Implantation: the "embedding" of the embryo in the uterine tissue, allowing it to establish contact with the mother's blood supply for nourishment. Implantation usually occurs 5 to 10 days after ovulation.

IVF treatment or in vitro fertilisation: a fertility treatment involving the collection of the egg and the sperm and the fertilisation of the egg in a test-tube. Once fertilised, the egg is replaced into the woman's womb. IVF literally means "fertilisation in a glass tube".

LH, or luteinising hormone: a pituitary hormone which stimulates the gonads. In women, LH induces the production of estrogens by the ovaries and the high levels of LH mid-cycle trigger the release of enzymes which allow the egg to be released from the follicle (ovulation).

Libido: sexual desire.

Luteal phase: the post-ovulatory phase of the menstrual cycle. During this phase, the corpus luteum (or yellow body) produces progesterone, and the endometrium (uterine lining) thickens to support the implantation and growth of the embryo.

Menstrual cycle: the period of time lasting from the first day of your menstruation to the day before your next menstruation (period). During each menstrual cycle, an egg is usually released.

Menstruation or period: the cyclical shedding of the endometrium (uterus lining), which occurs about two weeks after ovulation.

Oestrogens: the group of female sex hormones. The principal oestrogen involved in fertility is oestradiol. Oestrogens are mainly secreted by the ovaries, but they can also be produced by adipose tissue (fat).

Ovarian follicle: a fluid-filled structure inside the ovary which contains the egg. During each cycle, an egg develops within a follicle inside the ovary. This follicle grows up to 2 cm in diameter until it is ready to release the egg.

Ovulation: the release of the egg from the ovarian follicle. This occurs between the follicular and the luteal phases of the menstrual cycle.

Pituitary: a gland located at the base of the brain near the hypothalamus. The pituitary secretes several hormones including gonadotrophins (LH and FSH) in response to the hormonal stimulation of the hypothalamus (GnRH).

Progesterone: the hormone produced by the corpus luteum after ovulation and during pregnancy. It has a role in inhibiting the development of further follicles and in the thickening of the endometrium (uterus lining). It is secreted in a pulsatile fashion.

Careline

We understand that you may need advice or reassurance while you are using DuoFertility from someone who is familiar with the device and how it is designed. The DuoFertility careline has been set up to fulfil this need and offers free support for all DuoFertility users. Our highly trained staff will be happy to help you and answer any questions you may have about using the device.

If you have any specific questions about your cycles or fertility in general, for example, if you would like assistance interpreting your temperature graph or are worried about a potential fertility problem, we have an in-house team of highly qualified fertility experts who will be happy to answer any questions that you may have.

CARELINE: +44 1223 437003
Mon-Fri – 9:00 a.m – 6:00 p.m

From time to time we may monitor calls to the DuoFertility careline for training purposes.

You may also find the answers to your questions on our website:

www.DuoFertility.com

Name and address of manufacturer

Cambridge Temperature Concepts Limited is a UK registered company (number 5943341), with registered offices at Downing Enterprise, Downing College, University of Cambridge, Regent Street, Cambridge CB2 1DQ, United Kingdom.

The head offices are based at the Innovation Centre of Cambridge Science Park, Unit 23 Milton Road, CB4 0EY, Cambridge, UK.

Expiry date: The battery life of the sensor is estimated to be 3 to 6 months and the battery cannot be replaced. The lifetime of the reader is 3 years. The lifetime of the adhesive patch is indicated on the bag in which the adhesives are contained.

Specific Claims

The device is intended to give an indication of the user's body basal temperature. The device is not intended for use as a thermometer nor as a contraceptive aid. DuoFertility should not be used by those who are experiencing psychological disorders.

Temperature measurement is accurate to 0.1 degrees Celsius.

The manufacturer (CTC) has adopted the most appropriate solution for the manufacturing and design technology used for the DuoFertility device in order to reduce risks for the patient as far as possible. The only residual risk of the use of DuoFertility is possible irritation to the skin from wearing the adhesive. However, CTC has used a well known medical adhesive manufacturer who has tested their product for continuous skin contact of 29 days with no irritation reported.

Careline 01223 437003
support.en@duofertility.com

Manufactured and distributed by:
Cambridge Temperature Concepts Ltd.
23 Cambridge Science Park
Milton Road
Cambridge
CB4 0EF
United Kingdom

(b)(4) CCI

(b)(4) CCI (DOSAGE VOLUMES)

(b)(4) CCI [redacted]

Penny Northcutt RAC, FRAPS, CQA
REGSolutions, LLC

April 16, 2013

Dear Ms. Northcut,
The following statements are regarding the FDA response questions, Q9a and Q9b, to a submission of (b)(4) CCI [redacted] study reports by Fertility Focus.

FDA Question 9 for Biocompatibility

(b)(4) CCI [redacted]

FDA Question Q9a. Please provide the results of the Subchronic (b)(4) CCI [redacted] Toxicity Study assessed at (b)(4) CCI [redacted]

(b)(4) CCI [redacted]

ATTACHMENT Q12-1
REVISED INDICATION FOR USE FORM

Indications for Use

510(k) Number (if known): K122337

Device Name: **Fertility Focus OvuSense Fertility Monitor**

Indications for Use:

The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Prescription Use _____ AND/OR Over-The-Counter Use __X___

(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)

ATTACHMENT Q12-2
REVISED 510(K) SUMMARY

510(k) Summary

This 510(k) summary of safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

DATE:	July 30, 2013
APPLICANT:	Fertility Focus Ltd. Robert Milnes, CEO Unit 19D, University of Warwick Science Park Warwick Technology Park, Gallows Hill Warwick, United Kingdom CV34 6UW Tel: 044-1494-510272 Email: robert.milnes@fertility-focus.com
OFFICIAL CORRESPONDENT FOR THIS SUBMISSION:	Penny Northcutt, RAC, FRAPS, CQA Regulatory Consultant for Fertility Focus REGSolutions, LLC Tel: 678-428-6978 Fax: 678-513-0937 Email: pennynorthcutt@theregsolutions.com
TRADE NAME:	Fertility Focus OvuSense Fertility Monitor
CLASSIFICATION NAME:	Device, fertility diagnostic, proceptive
DEVICE CLASSIFICATION AND PRODUCT CODE:	Pre-amendment, Unclassified Product Code: LHD
PREDICATE DEVICE NAME:	DuoFertility Monitor, K102499 Bioself 2000 Fertility Indicator, K904211

SUBSTANTIAL EQUIVALENCE:
The Fertility Focus OvuSense Fertility Monitor is substantially equivalent to the legally marketed DuoFertility Monitor (K102499) and the Bioself 2000 Fertility Indicator (K904211). The Fertility Focus OvuSense Fertility Monitor has similar indications for use statements, principles of operation, and technological characteristics as the predicate devices.

510(k) Summary

DESCRIPTION OF THE DEVICE:
The Fertility Focus OvuSense Fertility Monitor is intended for measuring and recording core body temperature intra-vaginally on a nightly basis during the non-menstruating phases of the monthly female reproductive cycle. The Fertility Focus OvuSense Fertility Monitor consists of two components made of silicone - a Personal Sensor, which collects the data, and a Reader (with LCD display), which establishes a communication link to the Personal Sensor whereupon the data is transferred to the Reader.

Electromagnetic induction communications hardware transmits the stored temperature data from the Personal Sensor to the receiving device, the Reader, activated when the Sensor is placed on the Reader cradle and the Reader's dedicated download button is pressed. The microprocessor based Reader filters the overnight data, then calculates and stores the 25th percentile value, representative of the average basal (lowest) overnight temperature.

The Reader then displays these nightly temperature readings on a graph using a relative scale – the key information for necessary calculations being the temperature changes relative to other recorded temperatures within a cycle for a particular user, and not absolute temperature value. At the start of the next cycle, indicated by the User inputting first day of the bleeding in the cycle, the Reader algorithm calculates the date of ovulation in the prior cycle, and uses this to predict the fertile period for the cycle which has just started. The Reader then displays fertility information in a verbal summary, including:

- An indication of the day ovulation occurred in the prior cycle, or if ovulation was not detected it displays this information instead.
- An indication whether the cycle length was within the expected normal parameters.

INTENDED USE/INDICATIONS FOR USE:
The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

TECHNOLOGICAL CHARACTERISTICS:
OvuSense Fertility Monitor and DuoFertility Monitor have the following similar and substantially equivalent technological characteristics:

- Operating Principle – Both devices assess Basal Body Temperature.
- Temperature Sensor – Both devices use a thermistor sensor.
- Sensor Accuracy – The DuoFertility device has a quoted accuracy of +/- 0.05 degrees Centigrade, and of +/- 0.1 degrees Celsius; OvuSense Fertility Monitor has an accuracy of +/- 0.05 degrees Centigrade. Any potential difference in the accuracy of temperature measurements is not believed to raise any issues of safety, and is a function of the requirements of each devices' algorithms.
- User Inputs – Both devices have the facility for user input of relevant data.
- Display of Graphs – Both devices have the facility for the display of temperature graphs. The DuoFertility device uses a computer for this display and uses an absolute temperature scale, whilst OvuSense Fertility Monitor uses the OvuSense Reader for

display and a relative temperature scale. The different display methodologies do not raise any safety issues, with the relative temperature scale allowing the OvuSense Fertility Monitor user a graph view optimized to their particular temperature readings.

- Number of Measurements – Both devices record multiple temperatures. The difference in any relative number of temperature measurements is not believed to raise any issues of safety, and is simply a function of the requirements of each devices' algorithms.
- Automatic measurements – Both devices take measurements automatically.
- Wireless transfer of data – Both devices involve the transfer of data from the Sensor to a receiving unit.
- Algorithm – Both devices use an algorithm to calculate the date of ovulation. The additional information provided by the OvuSense Fertility Monitor device in respect of absence of ovulation and fertile period prediction is not believed to raise any direct issues of safety, and is employed for increased effectiveness.

The following differences between DuoFertility and OvuSense Fertility Monitor are noted and thus a secondary predicate or reference device – Bioself 2000 is used for substantial equivalence purposes.

- Number of Thermistors – The DuoFertility device uses two thermistors plus an accelerometer/movement Sensor; the OvuSense Fertility Monitor device uses a single thermistor. The Bioself 2000 device uses a single thermistor.
- Location of Thermistor – The DuoFertility device is worn on the skin; the OvuSense device is placed intravaginally by means of a Personal Sensor. The Bioself 2000 device can be used intravaginally or orally.

The use of two thermistors and an accelerometer (in DuoFertility) versus the use of a single thermistor (OvuSense Fertility Monitor and Bioself 2000) is not believed to raise any direct issues of safety or effectiveness, and the relative location of vaginal versus skin placement is employed by OvuSense Fertility Monitor and Bioself 2000.

NONCLINICAL PERFORMANCE TESTING:
A series of performance tests was conducted in support of the design verification of the Fertility Focus OvuSense Fertility Monitor.

Summary of Performance Testing Conducted on OvuSense	
Biocompatibility	In Vitro Cytotoxicity MEM Elution Assay
	Mucosal (Vaginal) Irritation Test
	Guinea Pig Maximization Sensitization Test
	USP Physicochemical Extraction Parameters
	ISO Acute Systemic Toxicity Test
	In Vitro Mouse Micronucleus Assay – 2 Extracts (ISO)
	In Vivo Mouse Micronucleus Assay – 2 Extracts
	Bacterial Mutagenicity Test (Ames Assay)

510(k) Summary

Summary of Performance Testing Conducted on OvuSense	
	(b)(4) CCI [redacted]
	[redacted]
	[redacted]
Electrical Testing	(b)(4) CCI [redacted] electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.
	EN60601-1-2:2007 Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests
	EN301 489-3 v1.4.1 Electromagnetic Compatibility and Radio Spectrum Matters (ERM); ElectroMagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3: Specific Conditions for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz
	IEC60601-1:2006 Medical equipment. Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
	EN302 291 v1.1.1 Electromagnetic compatibility and Radio spectrum Matters (ERM); Short Range Devices (SRD); Close Range Inductive Data Communication equipment operating at 13,56 MHz; Part 2: Harmonized EN under article 3.2 of the R&TTE Directive
Mechanical Testing	Tensile (Pull Test)
Design Verification & Validation	Physical Dimensions, User Cleaning, Reliability for Operating Life, Human Factors-Machine Interface
Cleaning Validation	Cleaning Validation of Personal Sensor

CLINICAL TESTING:
Clinical investigation was conducted of the Fertility Focus OvuSense Fertility Monitor from 19 women who participated in a prospective study measuring 81 cycles over 3 months participation.

510(k) Summary

The data from the primary endpoint of the trial described in the CIP demonstrated that the OvuSense Fertility Monitor system of ovulation detection provided a biological and statistically significant improvement in ovulation detection compared with the traditional method of oral temperature measurement. (b)(4) CCI [redacted]

CONCLUSION:

Based on the nonclinical verification performance testing and clinical validation, it can be concluded that the Fertility Focus OvuSense Fertility Monitor is equivalent to the DuoFertility Monitor (K102499) and Bioself 2000 (K904211) with respect to intended use, principles of operation, and technological characteristics. The Fertility Focus OvuSense Fertility Monitor has been demonstrated to be as safe, as effective, and performs as well as or better than the predicates.

ATTACHMENT Q12-3
REVISED OVUSENSE LABELING

QUANTITY	1
LOT LOT CODE	
SN SERIAL NO.	
DATE OF MANUFACTURE	2012-07
DATE OF EXPIRATION	2014-07
SEE INSTRUCTIONS FOR USE	CE 0088 EUROPEAN CONFORMITY
STORE -20°C TO +50°C MAX 95% RELATIVE HUMIDITY (NON-CONDENSING)	

OvuSense™ Sensor

To be used with OvuSense Reader. The OvuSense Fertility Monitor is intended for measuring and recording body temperature on a nightly basis during phases of the monthly female reproductive cycle when the subject is not menstruating. OvuSense detects the presence and absence of ovulation, as well as predicting the fertile period for the next monthly cycle.

Manufactured by:

a Fertil ty Focus Limited
Unit 19D, Univers ty of Warw ck Science Park
Warw ck Innovation Centre, Gallows Hill
Warw ck CV34 6UW, Un ted Kingdom

t +44 (0) 1793 848088
f +44 (0) 1793 855440l
e serv ce@fertility-focus.com

w www.fertility-focus.com

THIS PRODUCT IS NOT FOR CONTRACEPTIVE USE

Conforms to ASTM E1113

fertility focus

M007-23JUL13–V3.0 USA

OvuSense Reader
English M010-US

The OvuSense (OvuSense Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Quantity	OvuSense Reader	1

Unit 19D
Univers ty of Warw ck Science Park
Warwick Innovat on Centre
Warwick Technology Park
Gallows Hill
Warwick
CV34 6UW
United Kingdom

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CE 0088

ATTACHMENT Q13-1
REVISED 510(K) COVER SHEET (FDA FORM 3514)
& ADDITIONAL CONSENSUS STANDARDS FORMS (FDA FORM 3654)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

Form Approval
OMB No. 9010-0120
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)
July 30, 2013	(b)(4)	K122337

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)*		
Fertility Focus Ltd	3006799946		
Division Name *(if applicable)*	Phone Number *(including area code)*		
	044-1494-510272		
Street Address Unite 19D, University of Warwick Science Park Warwick Innovation Center, Warwick Technology Park	FAX Number *(including area code)*		
City	State / Province	ZIP/Postal Code	Country
Gallows Hill	Warwick	CV34 6UW	United Kingdom
Contact Name			
Robert Milnes			
Contact Title	Contact E-mail Address		
CEO	robert.milnes@fertility-focus.com		

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

REGSolutions, LLC			
Division Name *(if applicable)*	Phone Number *(including area code)*		
	(678) 428-6978		
Street Address	FAX Number *(including area code)*		
717 Lakeglen Drive	(678) 513-0937		
City	State / Province	ZIP/Postal Code	Country
Suwanee	Georgia	30024	USA
Contact Name			
Penny Northcutt			
Contact Title	Contact E-mail Address		
President/CEO	pennynorthcutt@theregsolutions.com		

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

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

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

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

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

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

- ☐ Response to FDA correspondence:

- ☐ 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

- ☐ Repose 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

Summary of, or statement concerning, safety and effectiveness information

☒ 510 (k) summary attached

☐ 510 (k) statement

1	LHD	2		3		4		11
5		6		7		8		55

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

	510(k) Number	*Trade or Proprietary or Model Name*	*Manufacturer*
1	K102499	DuoFertility Monitor	Cambridge Temperature Concepts Ltd
2	K904211	Bioself 2000 Fertility Indicator	Bioself, Inc
3			
4			

SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

Common or usual name or classification

Device, fertility diagnostic, proceptive

	Trade or Proprietary or Model Name for This Device	Model Number
1	Fertility Focus OvuSense Fertility Monitor	Personal Sensor: M011 Reader: M010-US Starter Kit: M009-US (includes Reader M010-US and Personal Sensor M011)
2		
3		

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

3	3	3	3	3	3
9	9	9	9	9	9

Data Included in Submission

☒ Laboratory Testing ☐ Animal Trials ☐ Human Trials

SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

Product Code: LHD

C.F.R. Section *(if applicable)*:

Device Class

☐ Class I ☒ Class II ☐ Class III ☐ Unclassified

Classification Panel

Unclassified

Indications *(from labeling)*

The Fertility Focus OvuSense Fertility Monitor (Fertility Focus OvuSense Fertility Monitor Starter Kit M009-US, which includes Reader M010-US and Personal Sensor M011) is intended for measuring and recording basal body temperature (BBT) as an aid in ovulation prediction to aid in conception (not to be used for contraception).

Note: Submission of this information does not affect the need to submit a 2891 or a 2891a Device Establishment Registration form.	FDA Document Number (if known)

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

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

(b)(4) CCI

[redacted]

☒ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☒ Contract Manufacturer ☐ Repackager / Relabeler

Company / Institution Name	Establishment Registration Number		
Clinical Polymer Technologies Ltd			
Division Name *(if applicable)*	Phone Number *(including area code)*		
Street Address Gee Road Whitwick Business Park	FAX Number *(including area code)*		
City Coalville	State / Province Leicestershire	ZIP/Postal Code LE67 4NB	Country United Kingdom
Contact Name Garry Shaw	Contact Title Director	Contact E-mail Address garryshaw@clinipol.co.uk	

☐ Original ☐ Add ☐ Delete	FDA Establishment Registration Number	☐ Manufacturer ☐ Contract Sterilizer ☐ Contract Manufacturer ☐ 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/Postal 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
	ISO 14971	ISO	Application of Risk Management to Medical Devices		2007
	Standards No.	Standards Organization	Standards Title	Version	Date
	IEC 62304	IEC	Medical device software-Software life cycle processes		2006
	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 10993-10	ISO	Biological evaluation of medical devices – Part 10: Tests for irritation and delayed-type hypersensitivity		2002
	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 10993-5	ISO	Biological evaluation of medical devices – Part 5: Tests for In Vitro Cytotoxicity		2009
	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 10993-3	ISO	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity		2003
	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 10993-11	ISO	Biological evaluation of medical devices -- Part 11: Tests for systemic toxicity		2006
	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 10993-12	ISO	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials		2012

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:

Food and Drug Administration
CDRH (HFZ-342)
9200 Corporate Blvd.
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

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Additional Standards

	Standards No.	Standards Organization	Standards Title	Version	Date
	ISO 14155	ISO	Clinical investigation of medical devices for human subjects - Good clinical practice.		2011
	Standards No.	Standards Organization	Standards Title	Version	Date
	BS EN 60601-1-4	EN	Medical electrical equipment. General requirements for safety. Collateral standard. General requirements for electrical programmable medical systems.		2000
	Standards No.	Standards Organization	Standards Title	Version	Date
	ASTM E1112	ASTM	Standard Specification for Electronic Thermometer for Intermittent Determination of Patient Temperature		2011
	Standards No.	Standards Organization	Standards Title	Version	Date
	EN60601-1-2	ISO/EN	Medical Electrical Equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic Compatibility -- Requirements and tests		2001
	Standards No.	Standards Organization	Standards Title	Version	Date
	IEC60601-1	UL	Medical Electrical Equipment - Part 1: General Requirements for basic safety and essential performance		2006

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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 10993-3:2003/(R)2009, Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity, and reproduct

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-117	
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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-11:2006/(R)2010 Biological evaluation of medical devices -- Part (b): Tests for systemic toxicity

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-118	
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: ISO 10993-12:2007: Biological Evaluation of Medical Devices -- Part 12: Sample preparation and referenc

[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

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TYPE OF 510(K) SUBMISSION

☒ Traditional ☐ Special ☐ Abbreviated

STANDARD TITLE [1]

ISO 10993-12 Fourth edition 2012-07 Biological evaluation of medical devices - Part 12: Sample preparation and reference material

Please answer the following questions	Yes	No
Is this standard recognized by FDA [2]?	☒	☐
FDA Recognition number [3]	#2-191	
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).	☒	☐
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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: FDA Bluebook Memorandum G95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of

[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

ATTACHMENT Q14-1
POWER MEASUREMENTS FOR THE OVUSENSE SENSOR

(b)(4) CCI

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