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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 9 2001

The RxFiles Corporation
c/o Ms. Yolanda Smith
Smith Associates
P.O. Box 4341
Crofton, Maryland 21114

Re: K011571
Trade/Device Name: TRxF Intelligent Dosing System™
Regulation Number: 868.1890
Regulatory Class: II
Product Code: NDC
Dated: May 11, 2001
Received: May 21, 2001

Dear Ms. Smith:

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 (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). 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.

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. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, 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 sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4659. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

**510(k) Number (if known):** K011571

**Device Name**: TRxF Intelligent Dosing System™

**Classification Panel**: 868.1890

**Indications for Use:**
The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx™, InterchangeRx™ and PracticePrescribeRx™. The DoseRx™ is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRx™ is designed to switch a patient from one brand of agent to another while maintaining the therapeutic effect of the original agent. The PracticePrescirbeRx is a dosing simulator that offers graded prescriber training of next dose calculation scenarios with scalable patient response and surrogate marker inputs that allows the healthcare provider to gain guided and measured experience in calculating the next dose for a new or infrequently used drug.

The IDS™ is not a substitute for clinical reasoning. The IDS™ is an aid for trained clinicians based upon significant and properly entered data. Final drug dose recommendations for a patient must be made only after careful consideration of the full clinical status of the patient. No medical decision should be based solely upon the results provided by this software program.

**(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)**
**Concurrence of CDRH, Office of Device Evaluation (ODE)**

**Prescription Use** ✓ **OR Over-the-Counter Use**_____

(Division Sign-Off)
Division of General, Restorative
and Neurological Devices





**510(k) Number** K011571

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

Memorandum

Date: 8/13/01 DAH

From: DMC (HFZ-401)

Subject: Premarket Notification Number(s): K011571/A1

To: Division Director: SM/ dgmd

The attached information has been received by the 510(k) DMC on the above referenced 510(k) submission(s). Since a final decision has been rendered, this record is officially closed.

Please review the attached document and return it to the DMC, with one of the statements checked below.

_____Information does not change the status of the 510(k); no other action required by the DMC; please add to image file. (Prepare K-25) THIS DOES NOT APPLY TO TRANSFER OF OWNERSHIP. PLEASE BRING ANY TRANSFER OF OWNERSHIP TO POS.

_____Additional information requires a new 510(k); however, the information submitted is incomplete; (Noitify company to submit a new 510(k);[Prepare the K30 Letter on the LAN]

_____Additional information requires a new 510(k); please process [This information will be made into a new 510(k)

_____No response necessary (e.g., hard copy of fax for the truthful and accuracy statement, 510(k) statement).

**CLIA CATEGORIZATION refers to laboratory test system devices reviewed by the Division of Clinical Laboratory Devices (HFZ-440**

_____Information requires a **CLIA CATEGORIZATION**; the complexity may remain the same as the original 510(k) or may change as a result of the additional information (Prepare a CAT letter)

____Additional information requires a **CLIA CATEGORIZATION**; however, the information submitted is incomplete; (call or fax firm)

__✓__No response necessary

This information should be returned to the DMC within 10 working days from the date of this memorandum.

Reviewed by: DAH O.K. 9/12/01
Date: 8.10.01

Draft #2 : 9/8/99
Draft #3: 1/3/00

K011571/A

**Smith**

~ FDA CONSULTANTS ~

Specializing in Regulatory Affairs

August 9, 2001

Ms. Della Hammond
Food and Drug Administration
Office of Medical Devices
Document Control Center
9200 Corporate Center
Rockville, Maryland 20850

Ref: K011571
Device name: TRxF Intelligent Dosing System

Dear Ms Hammond:

The following is the information provided on the software verification and validation.

If you have any questions, please contact me at (888) 729-9674.

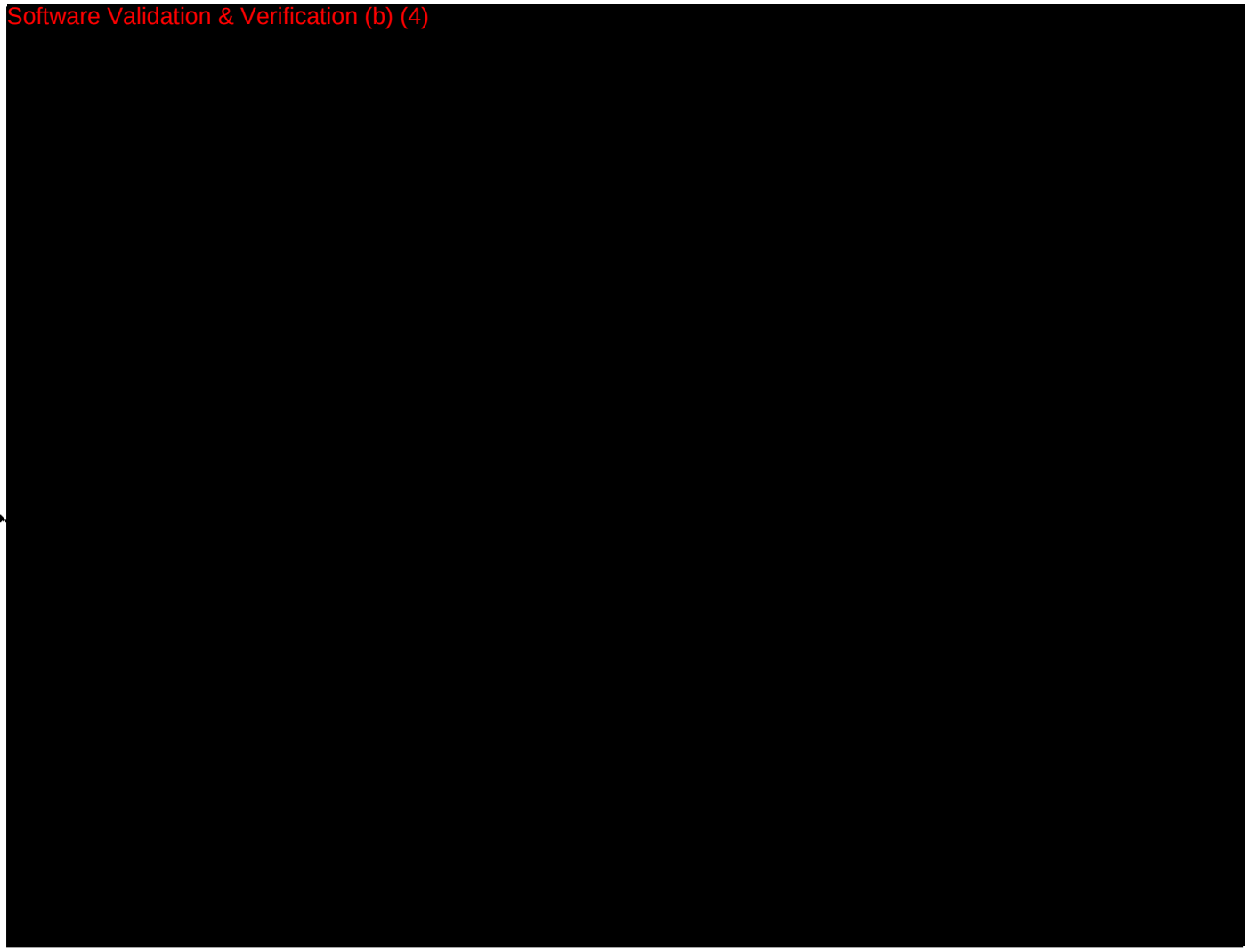
Sincerely,

Yolanda Smith

P.O. Box 4341 • Crofton, Maryland 21114
**PHONE:** (888) 729-9674 • **FAX:** (410) 793-0448
**WEB SITE:** www.fdaconsultants.com • **E-MAIL:** ESmith9746@aol.com

SK47 2

Software Validation & Verification (b) (4)



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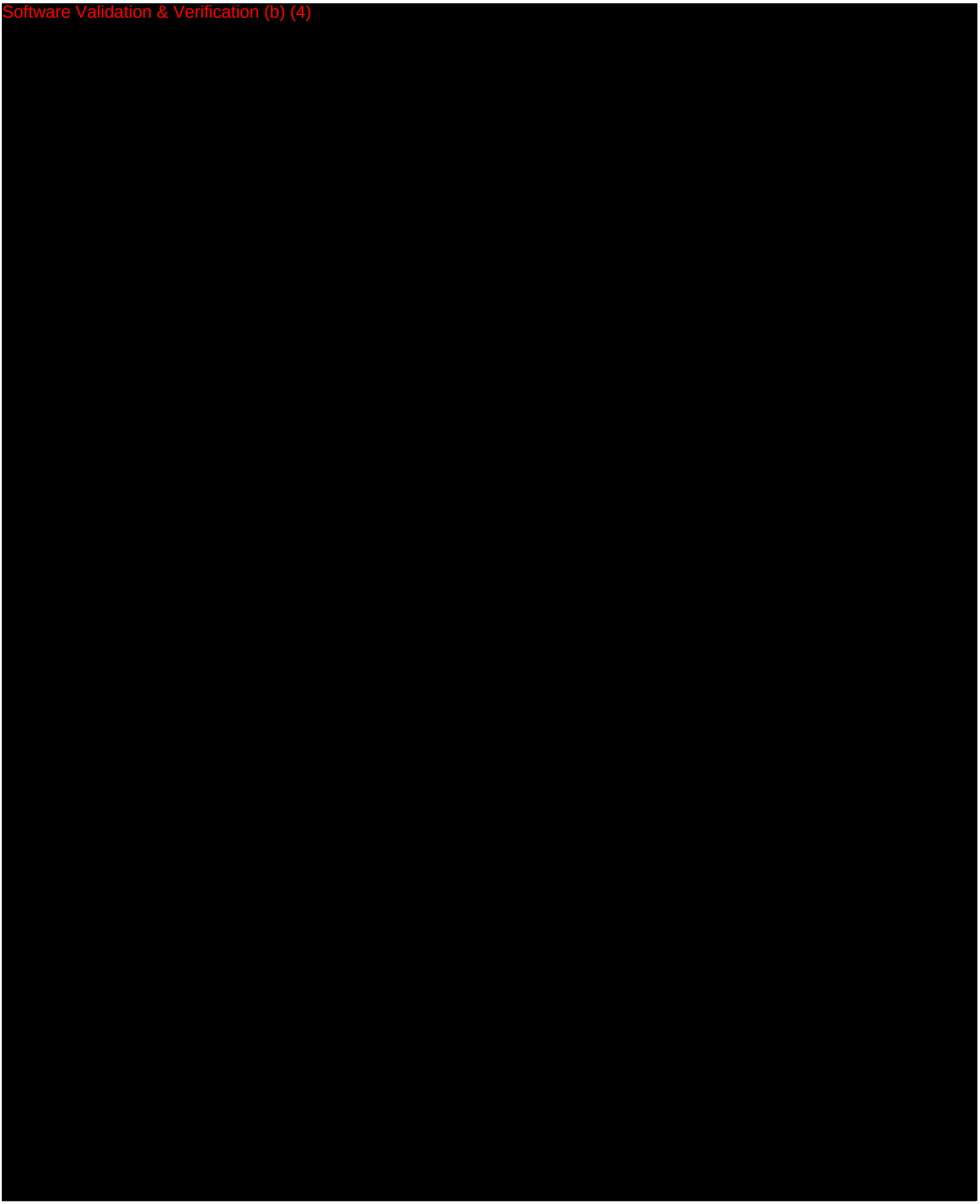

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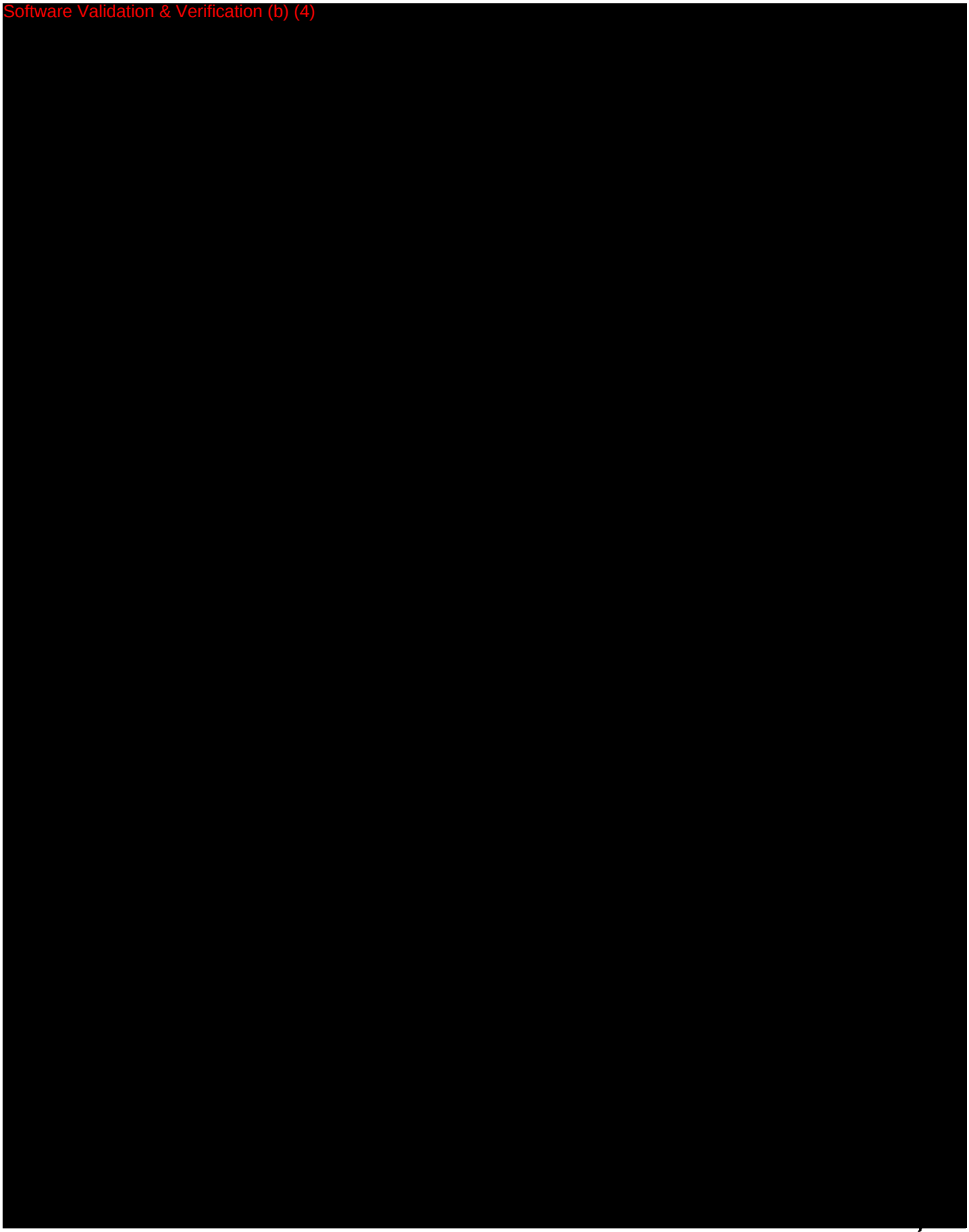

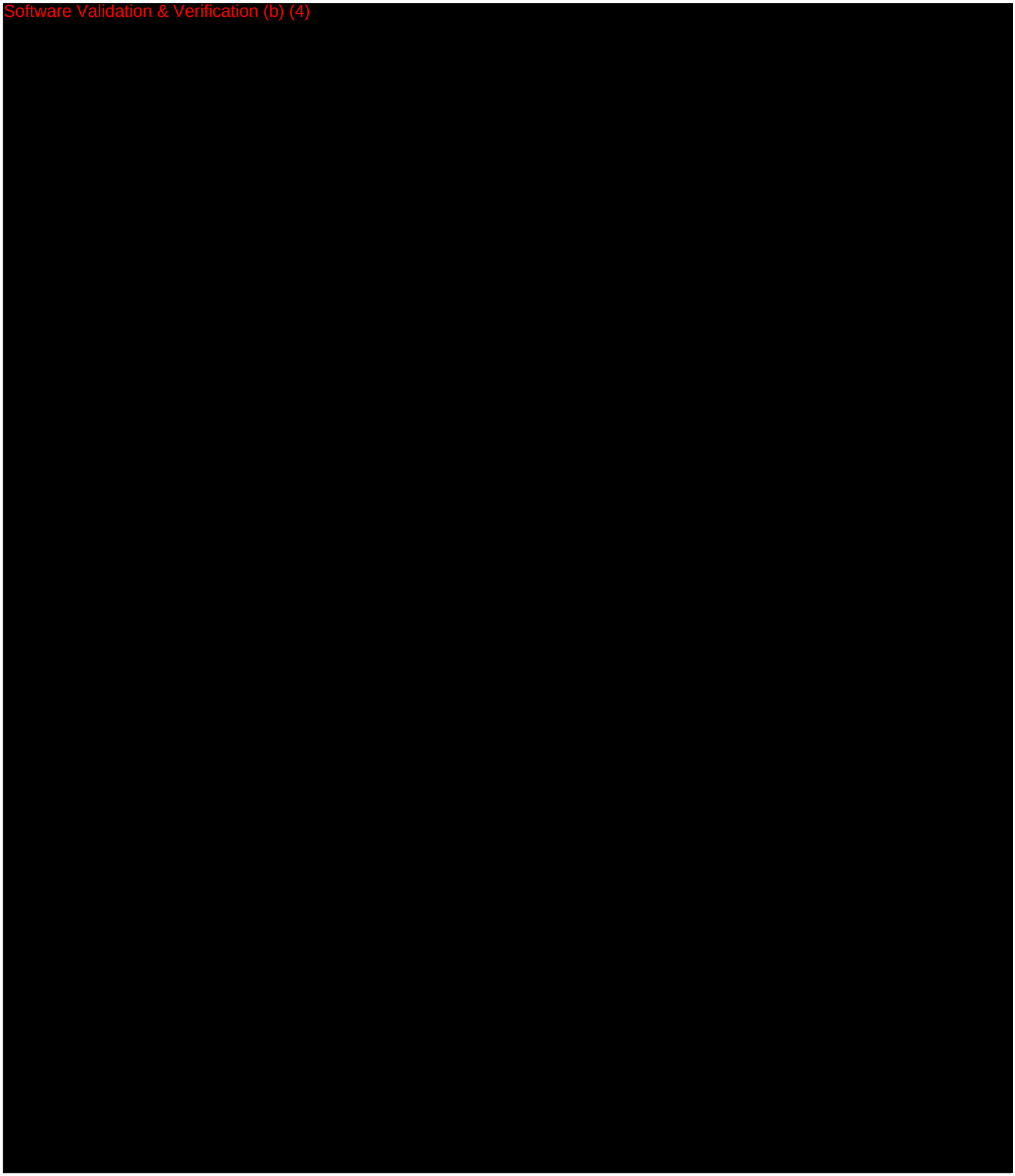

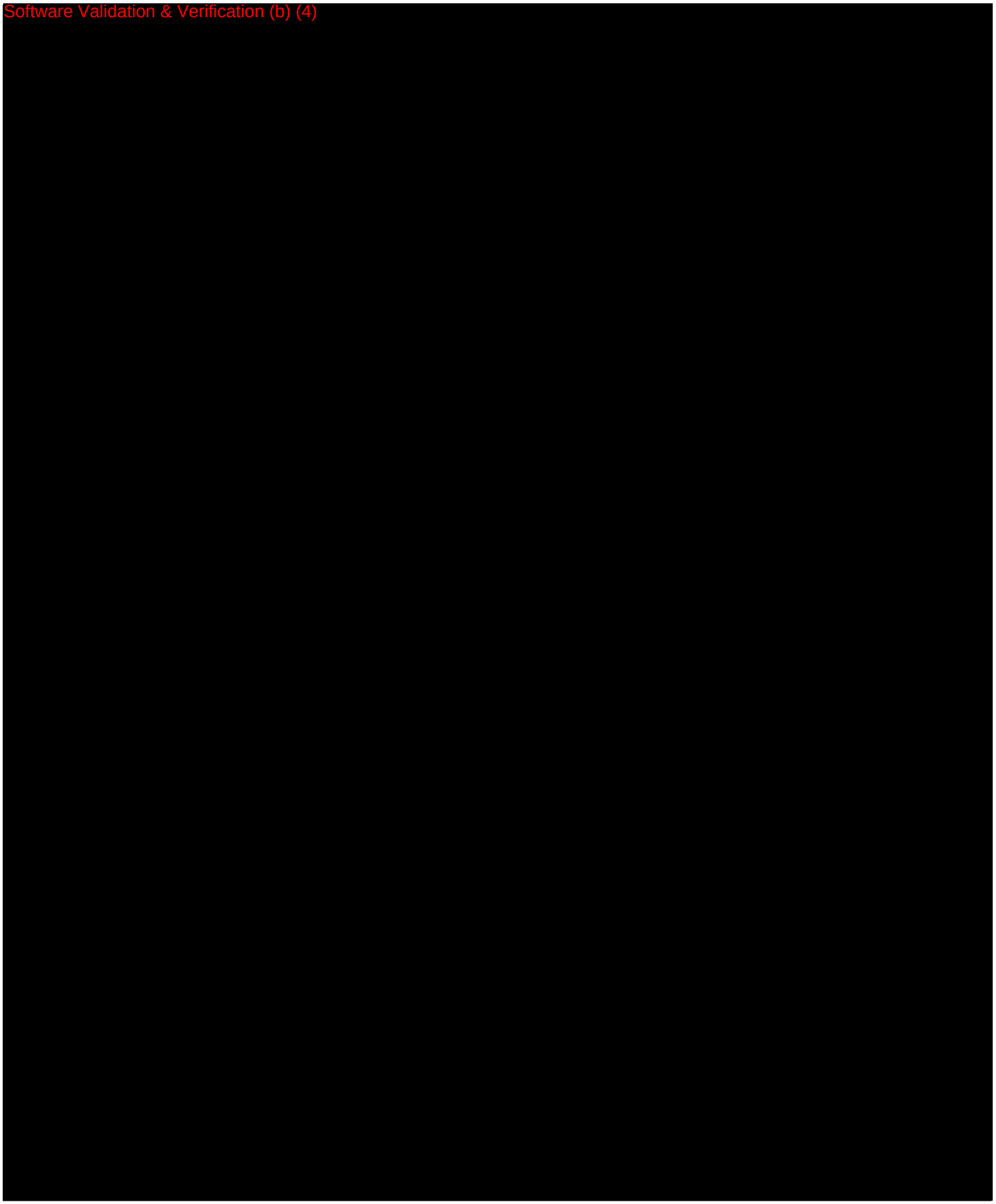

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Software Validation & Verification (b) (4)

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[redacted]

Software Validation & Verification (b) (4)

[redacted]

13

**Smith**

~ FDA CONSULTANTS ~

Specializing in Regulatory Affairs

August 9, 2001

Ms. Della Hammond
Food and Drug Administration
Office of Medical Devices
Document Control Center
9200 Corporate Center
Rockville, Maryland 20850

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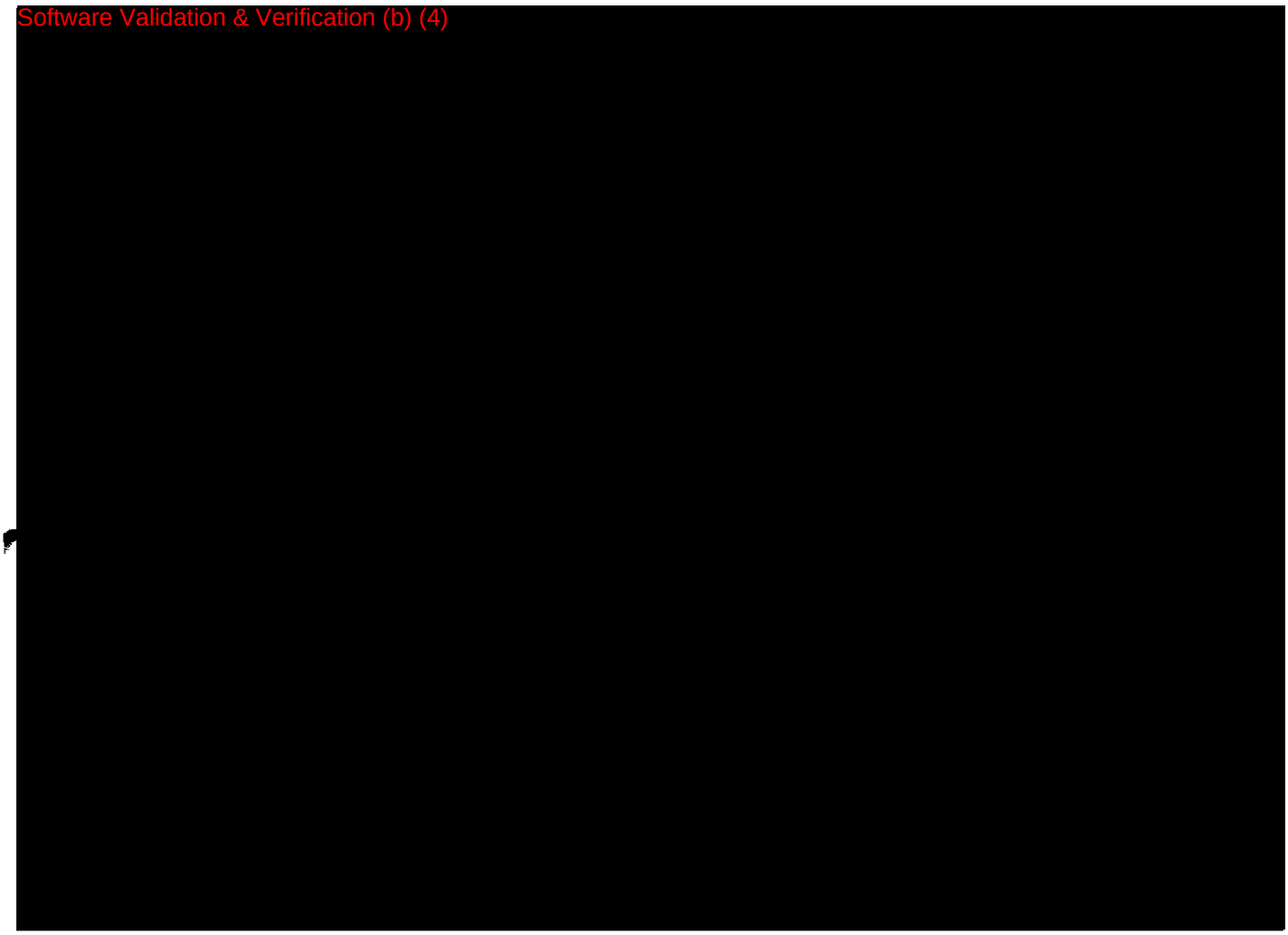


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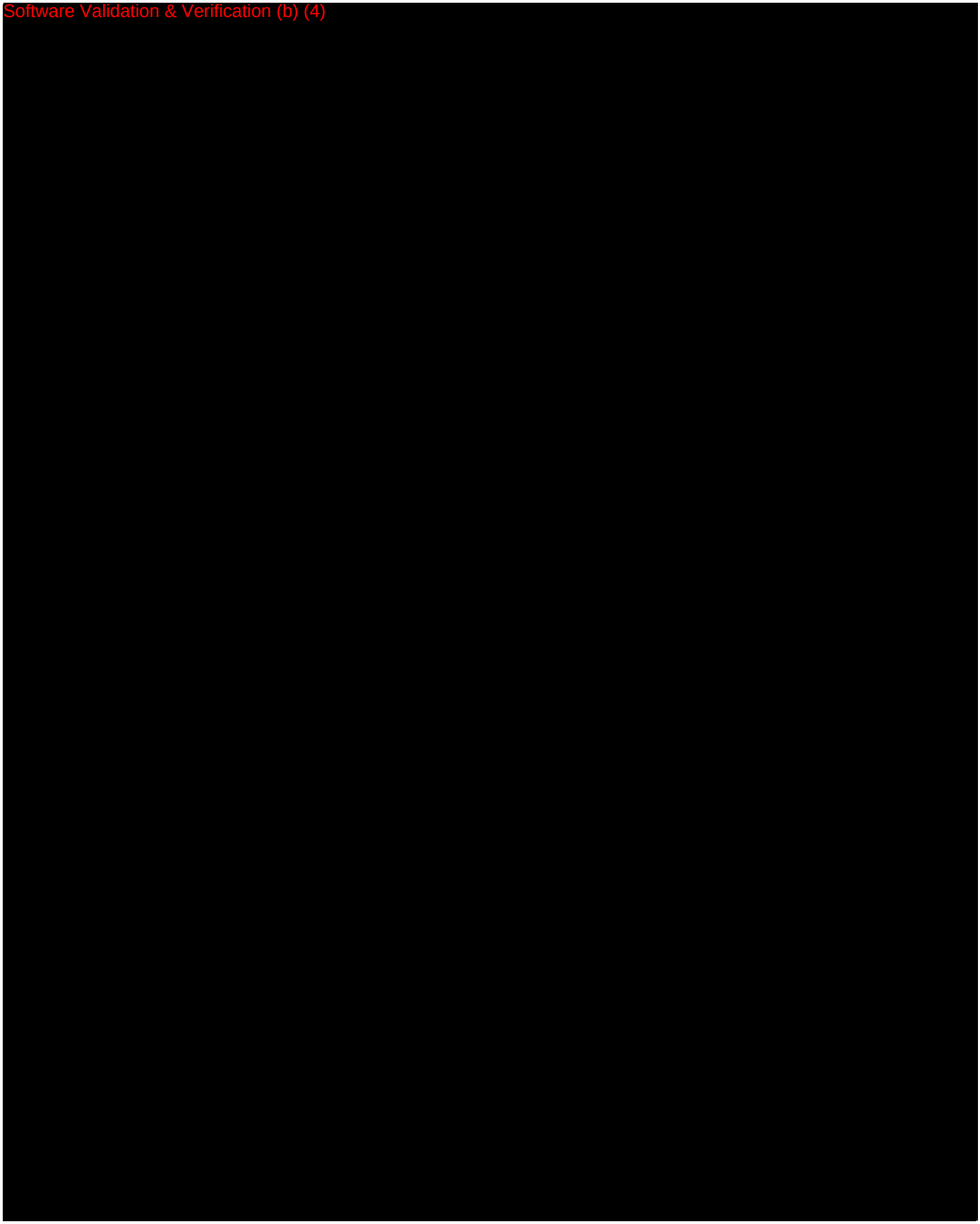
Software Validation & Verification (b) (4)



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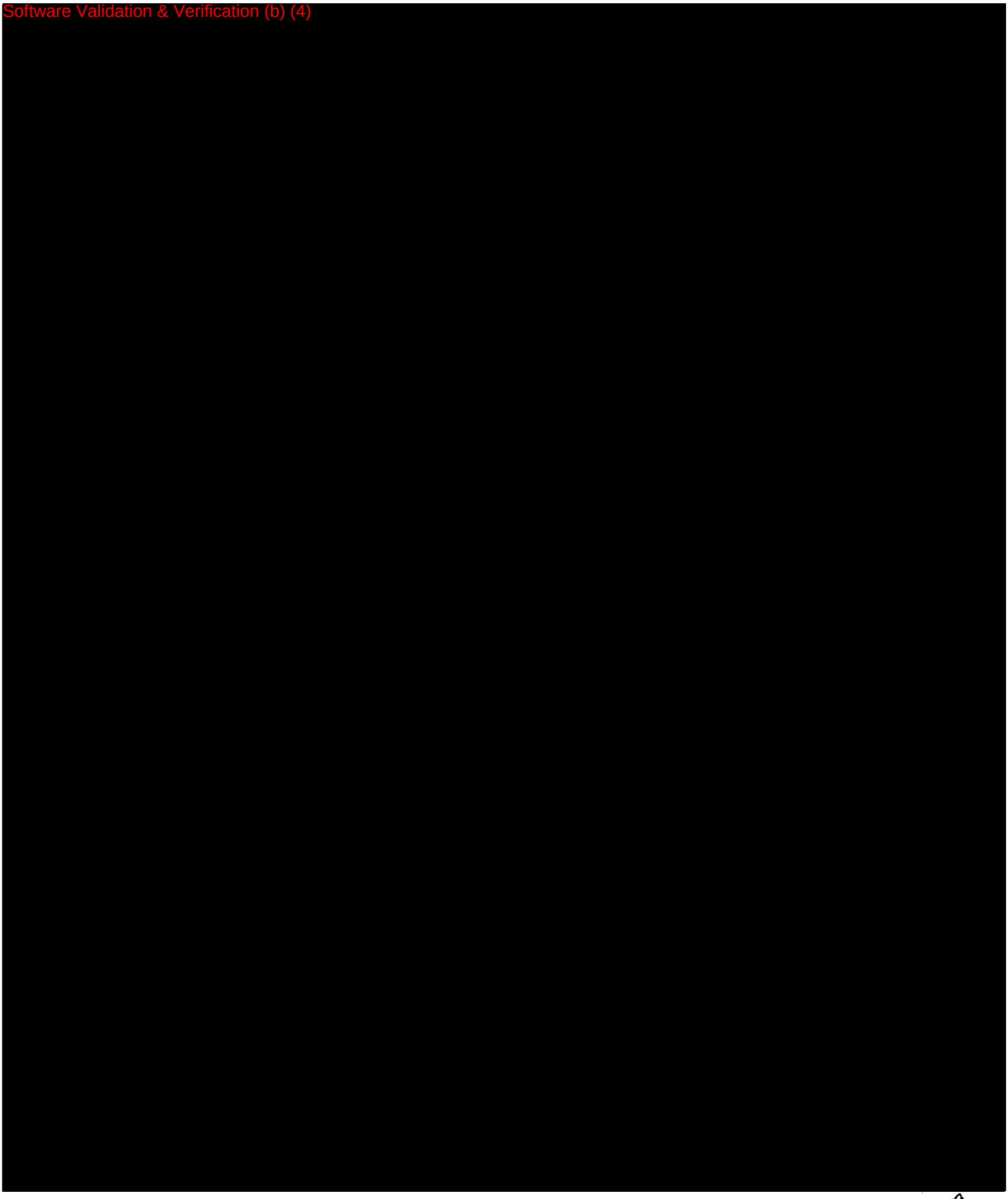

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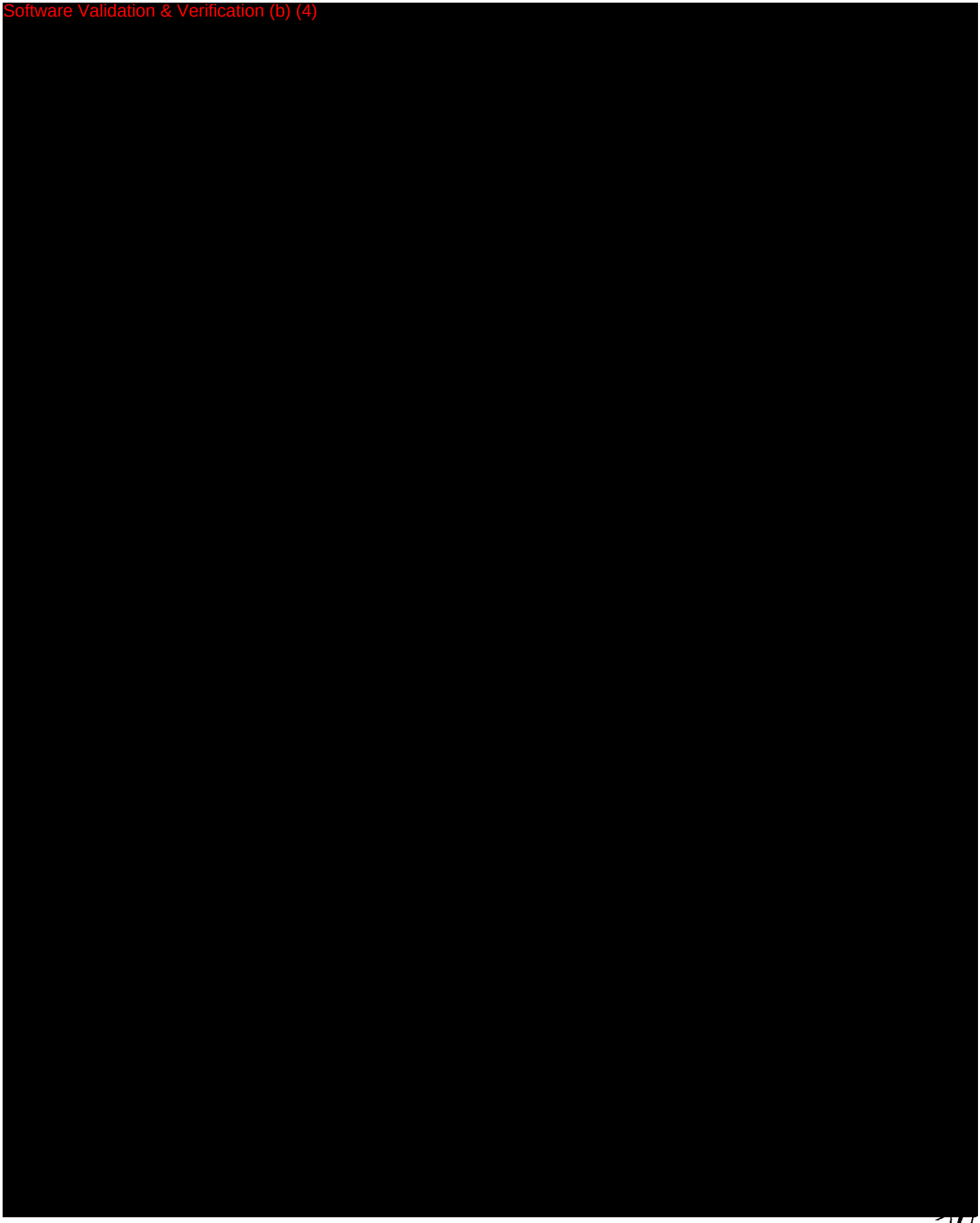

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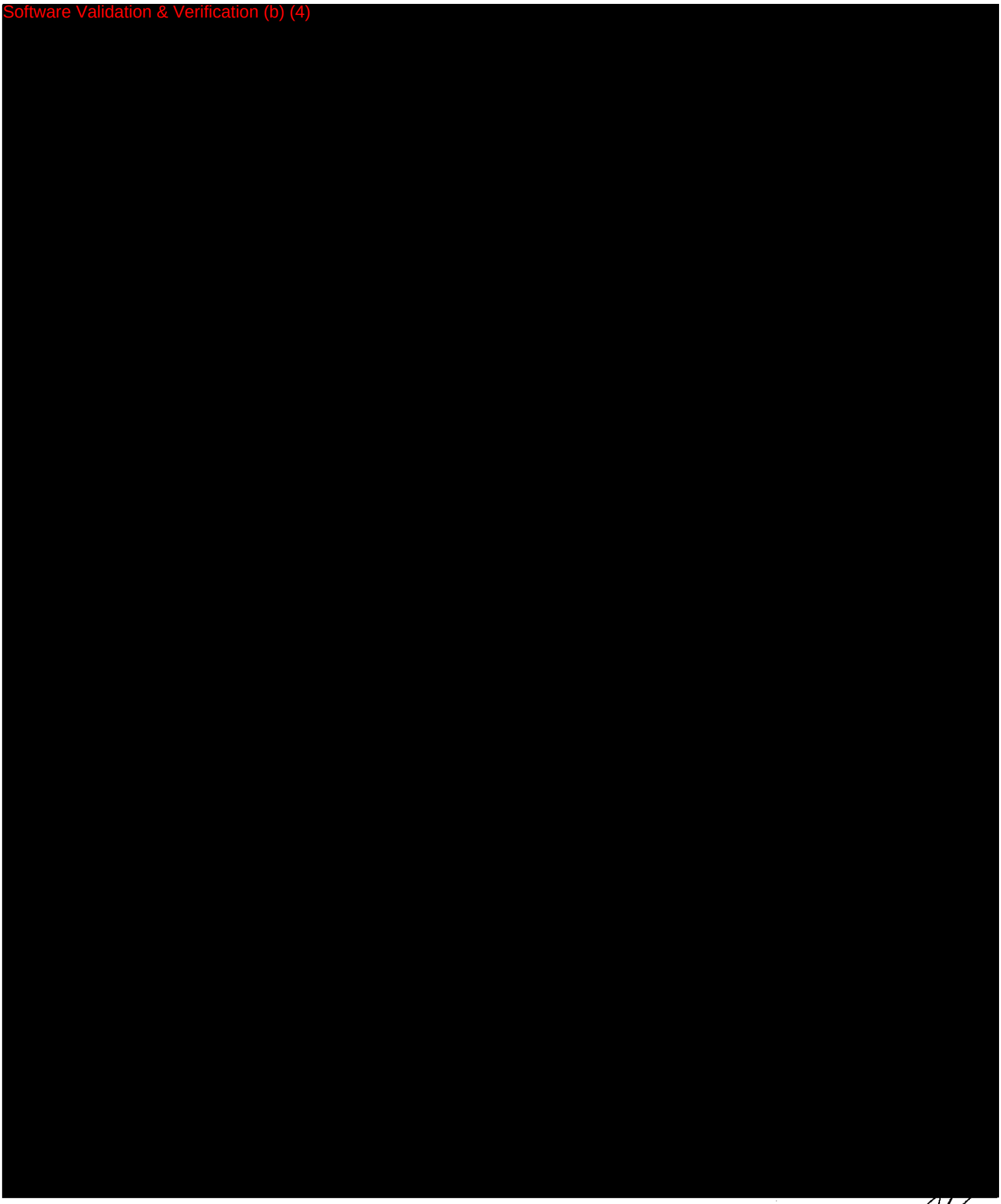

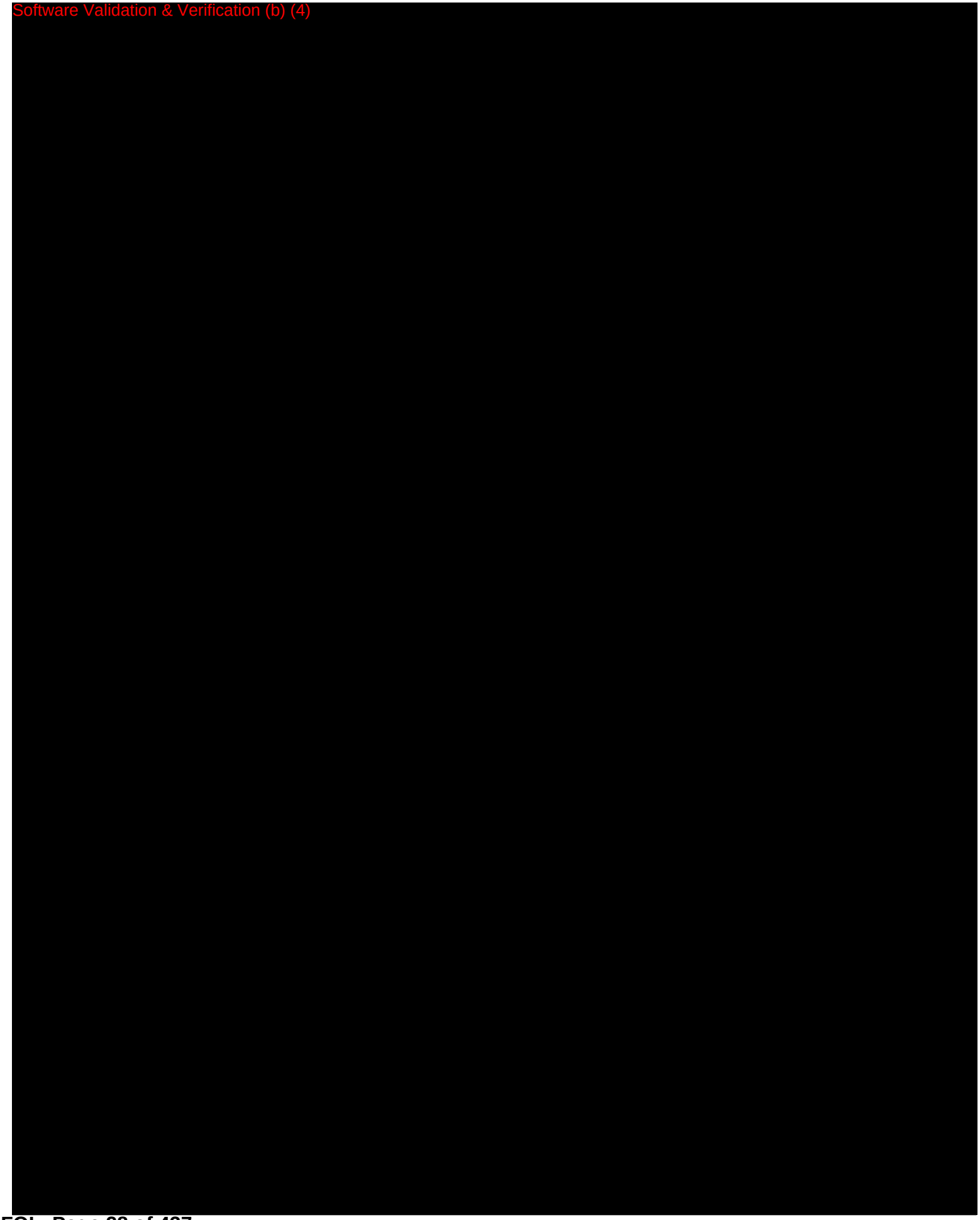

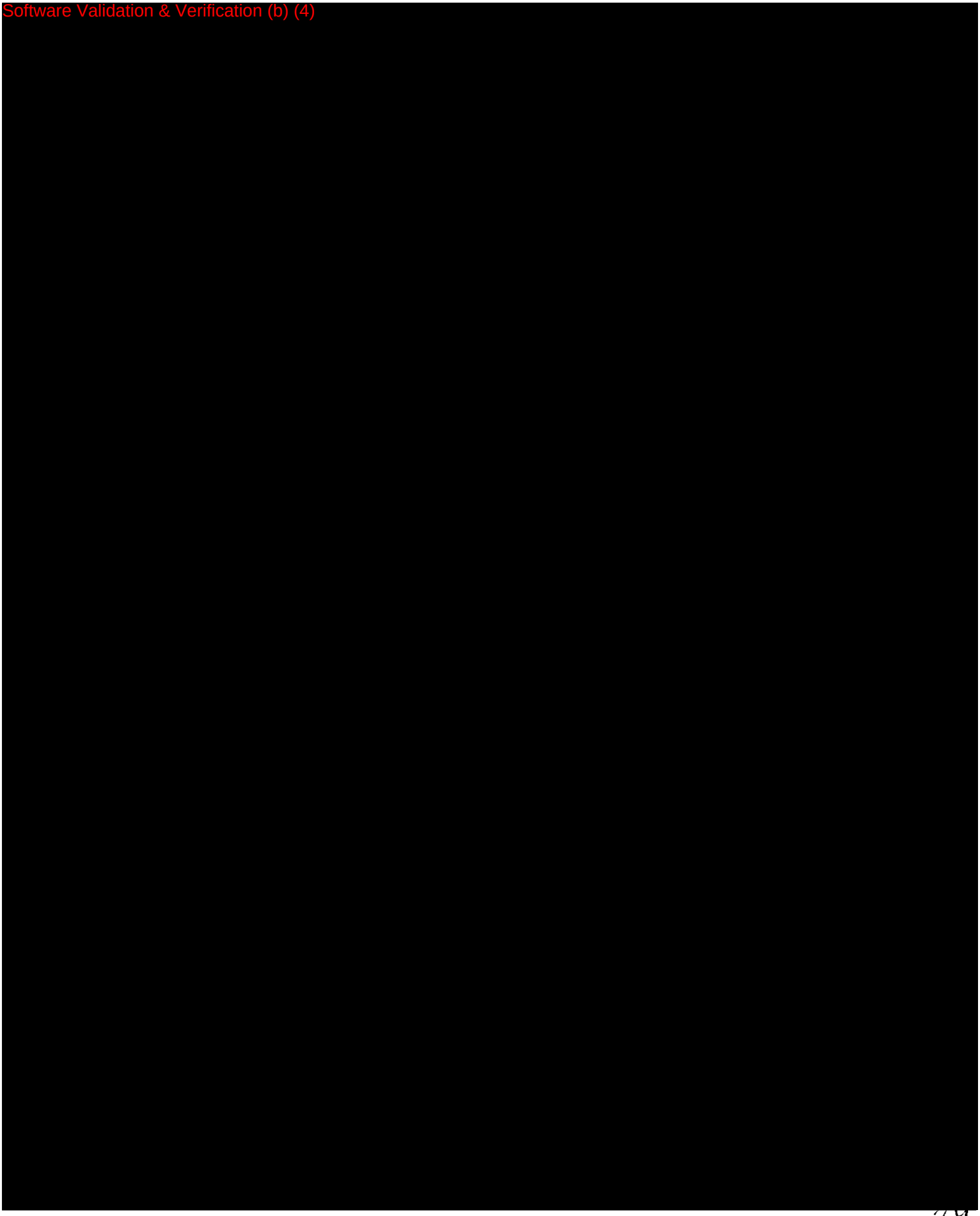

[redacted]

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Public Health Service

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AUG - 9 2001

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Product Code: NDC
Dated: May 11, 2001
Received: May 21, 2001

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Sincerely yours,

for Mark N. Melkerson

Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

**510(k) Number (if known):** K011571

**Device Name**: TRxF Intelligent Dosing System™

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**Concurrence of CDRH, Office of Device Evaluation (ODE)**

**Prescription Use** ✓ Mark A. Melkerson **OR** **Over the Counter Use** _____

(Division Sign-Off)
Division of General Restorative
and Neurological Devices





510(k) Number K011571

3

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

Memorandum

From: Reviewer(s) - Name(s) DELLA HAMMOND

Subject: 510(k) Number K 011571

To: The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☑ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☐ NO
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

| | | |
|---|---|---|
| Is this device subject to Postmarket Surveillance? | ☐ YES | ☑ NO |
| Is this device subject to the Tracking Regulation? | ☐ YES | ☑ NO |
| Was clinical data necessary to support the review of this 510(k)? | ☐ YES | ☑ NO |
| Is this a prescription device? | ☑ YES | ☐ NO |
| Was this 510(k) reviewed by a Third Party? | ☐ YES | ☑ NO |
| Special 510(k)? | ☐ YES | ☑ NO |
| Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers | ☐ YES | ☑ NO |

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☑ Enclosed
(required for originals received 3-14-95 and after)

- ☐ A 510(k) summary OR ☑ A 510(k) statement
- ☐ The required certification and summary for class III devices
- ☑ The indication for use form (required for originals received 1-1-96 and after)
- Material of Biological Origin ☐ YES ☑ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

☐ No Confidentiality ☐ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: NDC, II, 868.1890

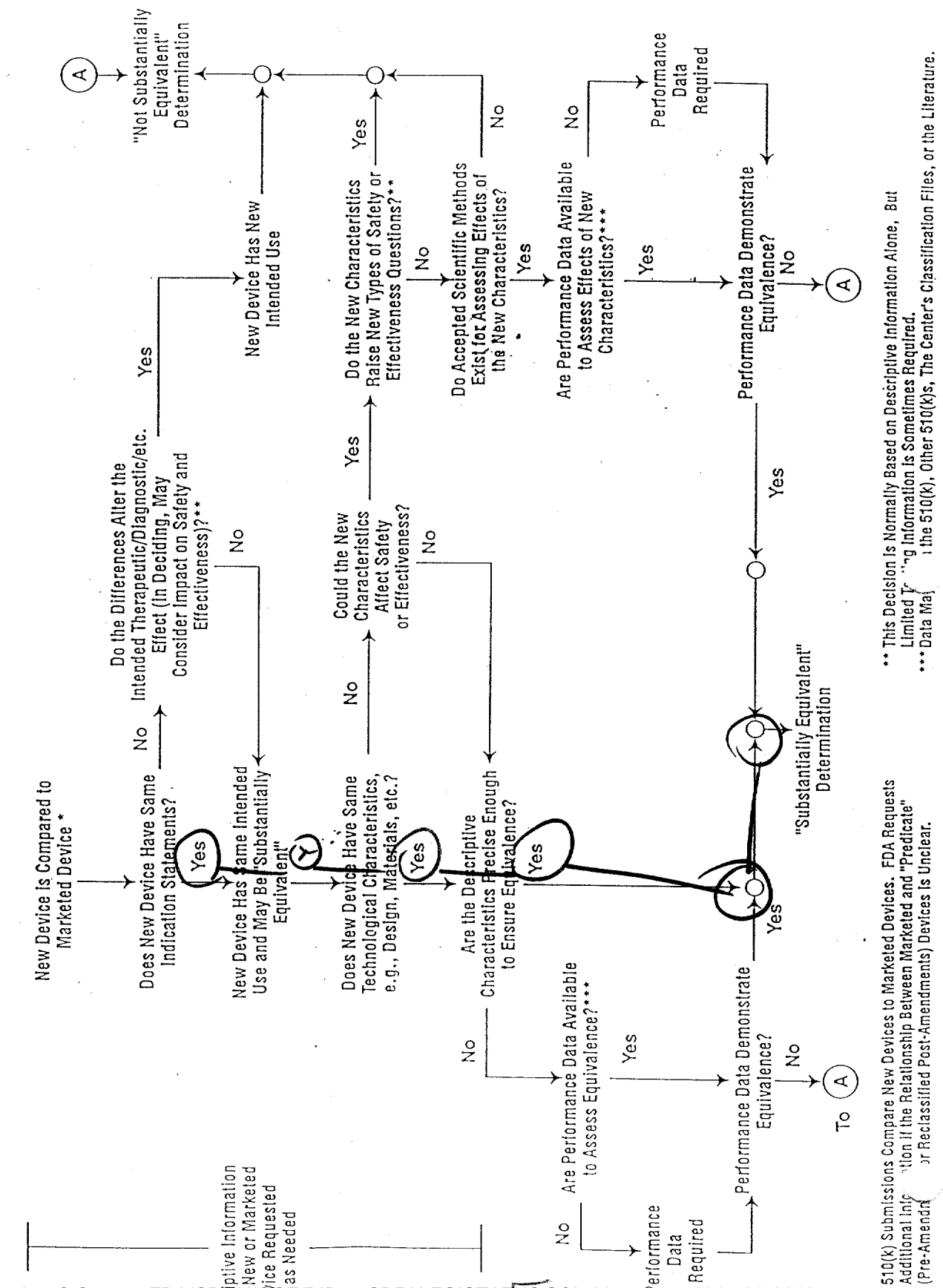
Additional Product Code(s) with panel (optional):

Review: [signature] (Branch Chief) GSDB (Branch Code) 8/3/01 (Date)

Final Review: [signature] for [signature] (Division Director) 8/9/01 (Date)

Revised: 8/17//99

# 510(k) "Substantial Equivalence" Decision-Making Process (Detailed)



# Screening Checklist
## For all Premarket Notification 510(k) Submissions

3-30-01

**Device Name:** TRFX INTELLIGENT DOSING SYSTEM (IDS) — K011571

**Submitter (Company):** THE RX FILES COMPANY

| Items which should be included *(circle missing & needed information)* | SPECIAL YES | SPECIAL NO | ABBREVIATED YES | ABBREVIATED NO | TRADITIONAL YES | TRADITIONAL NO | ✓ IF ITEM IS NEEDED AND IS MISSING |
|---|---|---|---|---|---|---|---|
| **1. Cover Letter clearly identifies Submission as:** a) "Special 510(k): Device Modification" b) "Abbreviated 510(k)" c) Traditional 510(k) | GO TO # 2,3 | | GO TO # 2,4,5 | | ✓ GO TO #2, 5 | | |

| **2. GENERAL INFORMATION: REQUIRED IN ALL 510(K) SUBMISSIONS** Financial Certification or Disclosure Statement for 510(k)s with a Clinical Study 807.87(i) including forms 3454 and/or 3455 | NA SPECIALS YES | NA SPECIALS NO | YES ABBREVIATED YES | YES ABBREVIATED NO | NO TRADITIONAL YES | NO TRADITIONAL NO | ✓ IF ITEM IS NEEDED AND IS MISSING |
|---|---|---|---|---|---|---|---|
| a) trade name, classification name, establishment registration number, device class | | | | | ✓ | | |
| b) OR a statement that the device is not yet classified | FDA-may be a classification request; see coordinator | | | | | | |
| c) identification of legally marketed equivalent device | NA | | | | ✓ | | |
| d) compliance with Section 514 - performance standards | NA | | | | ✓ | | |
| e) address of manufacturer | | | | | ✓ | | |
| f) Truthful and Accurate Statement | | | | | ✓ | | |
| g) Indications for Use enclosure | | | | | ✓ | | |
| h) SMDA Summary or Statement *(FOR ALL DEVICE CLASSES)* | | | | | ✓ | | |
| i) Class III Certification & Summary *(FOR ALL CLASS III DEVICES)* | | | | | | | |
| j) Description of device (or modification) including diagrams, engineering drawings, photographs, service manuals | | | | | ✓ | | |
| k) Proposed Labeling: | | | | | | | |
| i) package labeling (user info) | | | | | ✓ | | |
| ii) statement of intended use | | | | | ✓ | | |
| iii) advertisements or promotional materials | | | | | • | | |
| i) MRI compatibility (if claimed) | | | | | • | | |
| l) Comparison Information (similarities and differences) to named legally marketed equivalent device (table preferred) should include: | | | | | | | |
| i) Labeling | | | | | ✓ | | |
| ii) intended use | | | | | • | | |
| iii) physical characteristics | | | | | • | | |
| iv) anatomical sites of use | | | | | • | | |
| v) performance (bench, animal, clinical) testing | NA | | | | • | | |
| vi) safety characteristics | NA | | | | • | | |
| m) If kit, kit certification | | | | | • | | |

| **3. "SPECIALS" - ONLY FOR MODIFICATIONS TO MANUFACTURER'S OWN CLASS II , III OR RESERVED CLASS I DEVICE** | | | | |
|---|---|---|---|---|
| a) Name & 510(k) number of legally marketed (unmodified) predicate device | | | | |
| b) *STATEMENT - INTENDED USE AND INDICATIONS FOR USE OF MODIFIED DEVICE AS DESCRIBED IN ITS* | | | * If no - STOP not a special | |

| | | | | | | |
|---|---|---|---|---|---|---|
| any way(s) in which the standard may have been adapted for application to the device under review, e.g., an identification of an alternative series of tests that were performed | | | | | | |
| iv) An identification, for each consensus standard, of any requirements that were not applicable to the device | | | | | | |
| v) A specification of any deviations from each applicable standard that were applied | | | | | | |
| vi) A specification of the differences that may exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference | | | | | | |
| vii) Name/address of test laboratory/certification body involved in determining the conformance of the device with applicable consensus standards and a reference to any accreditations for those organizations | | | | | | |
| d) Data/information to address issues not covered by guidance documents, special controls, and/or recognized standards | | | | | | |

| **5. Additional Considerations: (may be covered by Design Controls)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation: | | | | | | | |
| i) component & material | | | | | - | | |
| ii) identify patient-contacting materials | | | | | - | | |
| iii) biocompatibility of final sterilized product | | | | | - | | |
| b) Sterilization and expiration dating information: | | | | | - | | |
| i) sterilization method | | | | | | | |
| ii) SAL | | | | | | | |
| iii) packaging | | | | | | | |
| iv) specify pyrogen free | | | | | | | |
| v) ETO residues | | | | | | | |
| vi) radiation dose | | | | | | | |
| c) Software validation & verification: | | | | | | | |
| i) hazard analysis | | | | | ✔ | | |
| ii) level of concern | | | | | ✔ | | |
| iii) development documentation | | | | | ✔ | | |
| iv) certification | | | | | ✔ | | |

***Items shaded under "NO" are necessary for that type of submission. Circled items and items with checks in the "Needed & Missing" column must be submitted before acceptance of the document.***

**Passed Screening** ✓ **Yes** ____ **No** **Reviewer:** [signature]

**Date:** 7.25.01 **Concurrence by Review Branch:** [signature]

REVISED:3/14/95

**THE 510(K) DOCUMENTATION FORMS ARE AVAILABLE ON THE LAN UNDER 510(K) BOILERPLATES TITLED "DOCUMENTATION" AND MUST BE FILLED OUT WITH EVERY FINAL DECISION (SE, NSE, NOT A DEVICE, ETC.).**

## "SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K 011571

Reviewer: DELLA HAMMOND

Division/Branch: DGRD/GSDB

Device Name: TRXF INTELLIGENT DOSING SYSTEM (IDS)

Product To Which Compared (510(K) Number If Known):

| | YES | NO | |
|---|---|---|---|
| 1. Is Product A Device | | | If NO = Stop |
| 2. Is Device Subject To 510(k)? | ✓ | | If NO = Stop |
| 3. Same Indication Statement? | ✓ | | If YES = Go To 5 |
| 4. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness? | | ✓ | If YES = Stop NE |
| 5. Same Technological Characteristics? | ✓ | | If YES = Go To 7 |
| 6. Could The New Characteristics Affect Safety Or Effectiveness? | | | If YES = Go To 8 |
| 7. Descriptive Characteristics Precise Enough? | ✓ | | If NO = Go To 10<br>If YES = Stop SE |
| 8. New Types Of Safety Or Effectiveness Questions? | | | If YES = Stop NE |
| 9. Accepted Scientific Methods Exist? | | | If NO = Stop NE |
| 10. Performance Data Available? | | | If NO = Request Data |
| 11. Data Demonstrate Equivalence? | | | Final Decision: SE |

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

# *Internal Administrative Form*

| | YES | NO |
|---|---|---|
| 1. Did the firm request expedited review?<br>2. Did we grant expedited review? | | ✓<br>✓ |
| 3. Have you verified that the Document is labeled Class III for GMP purposes?<br>4. If, not, has POS been notified? | | ✓<br>✓ |
| 5. Is the product a device?<br>6. Is the device exempt from 510(k) by regulation or policy?<br>7. Is the device subject to review by CDRH? | ✓ | ✓ |
| 8. Are you aware that this device has been the subject of a previous NSE decision?<br>9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)? | | ✓ |
| 10. Are you aware of the submitter being the subject of an integrity investigation?<br>11. If, yes, consult the ODE Integrity Officer.<br>12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991. | | ✓ |

(b)(4)

**Smith Associates**
P.O.. Box 4341 Crofton MD, 21114
Tel: (410)451-0639 Fax: 410(793-0448
E mail: YSmith9746@aol.com
Website: fdaconsultants.com

# FAX

**DATE: July 30, 2001**

**MEMO TO: Ms. Della Hammond**

**FAX NO.: 301-827-4350**

**FROM: Yolanda Smith**

**SUBJECT: RX Files (K011571)**

**No .of Pages _7__**

**Dear Ms Hammond:**

**The following is the information provided by RX Files on the software verification and validation.**

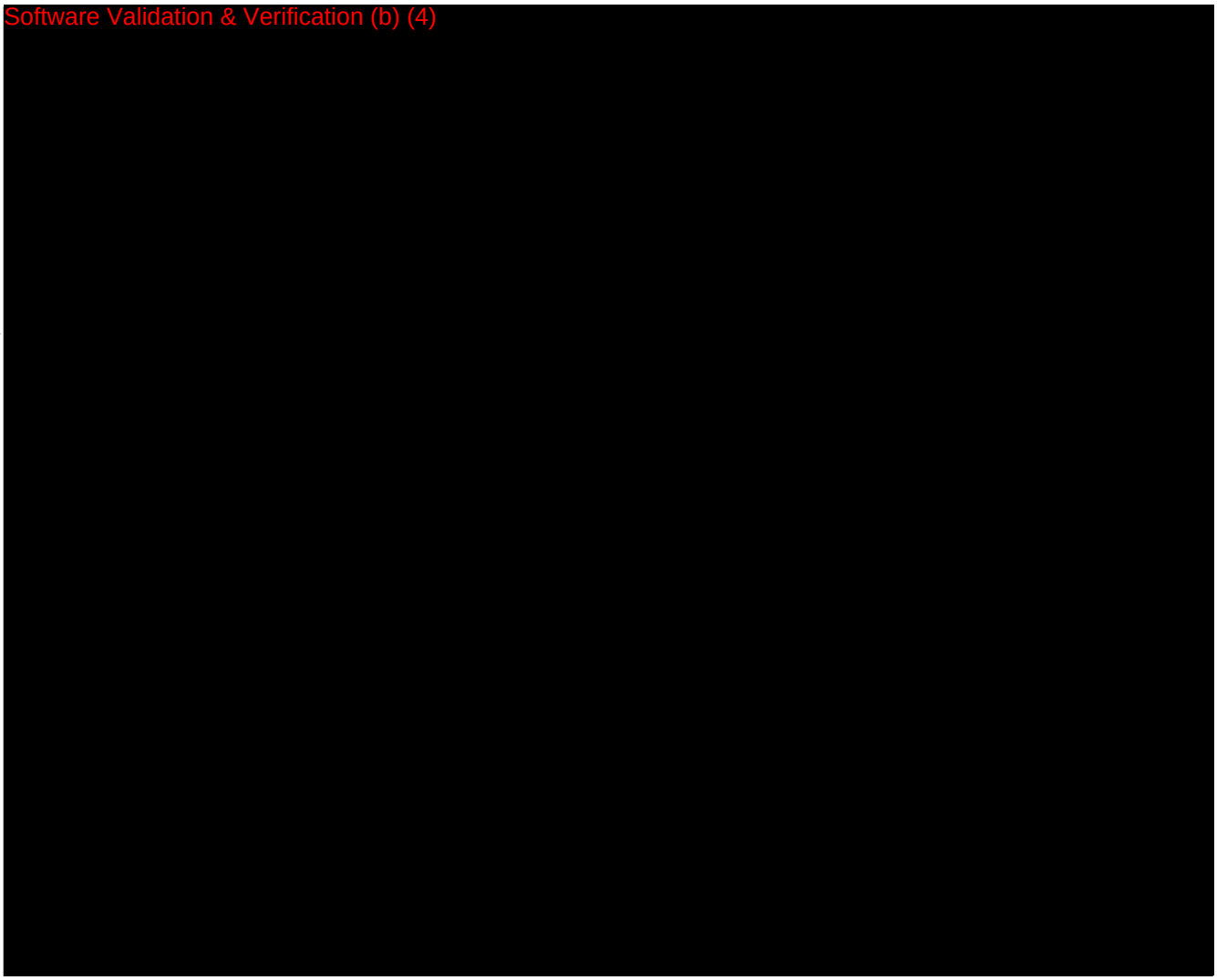
**If you have any questions, please contact me at (888) 729-9674.**

**Sincerely,**

**Yolanda Smith**

65

Software Validation & Verification (b) (4)



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Software Validation & Verification (b) (4)

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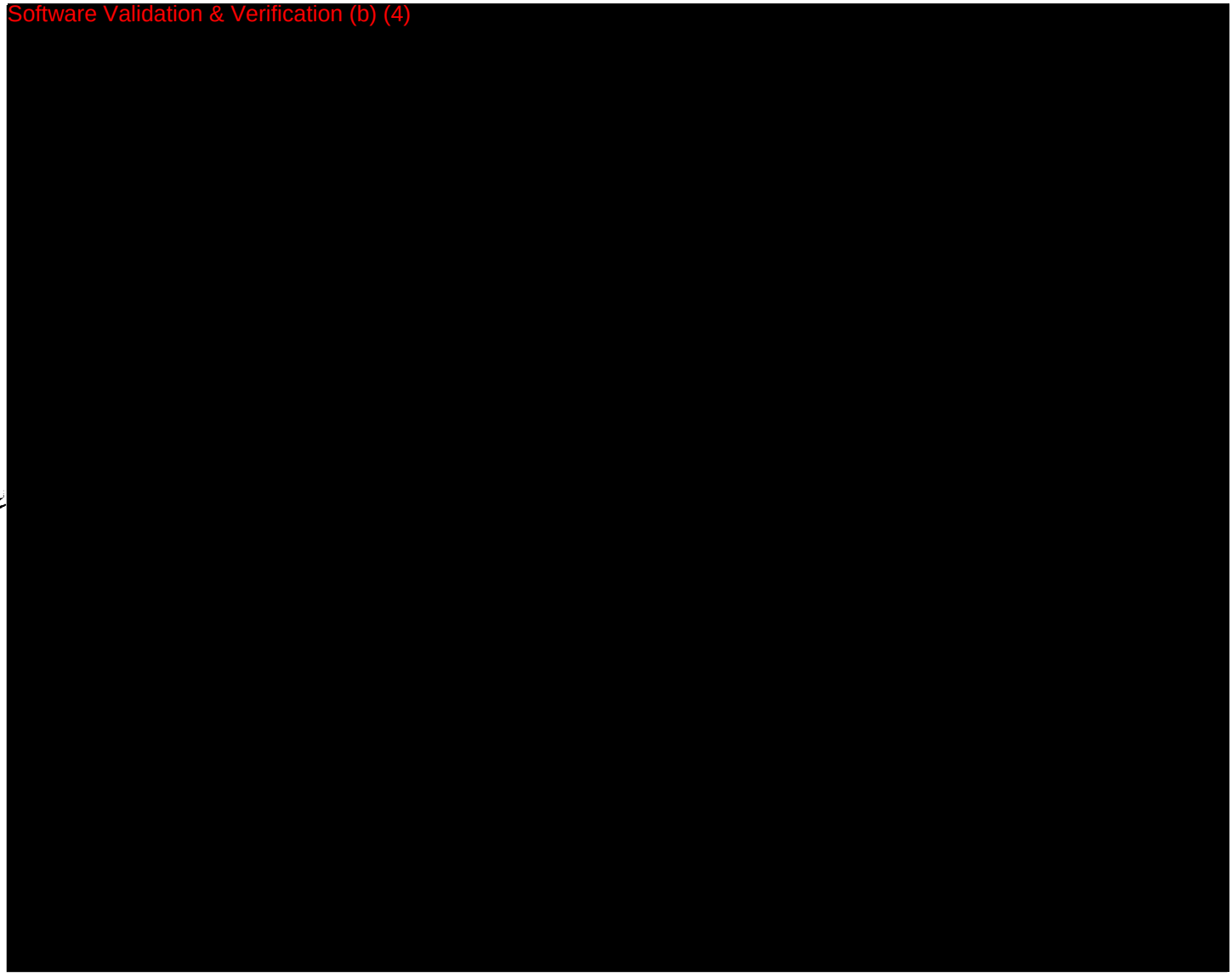
Software Validation & Verification (b) (4)



7/23/01

**Smith Associates**
P.O.. Box 4341 Crofton MD, 21114
Tel: (410)451-0639 Fax: (410)793-0448
E mail: YSmith9746@aol.com
Website: fdaconsultants.com

# FAX

**DATE: July 20, 2001**

**MEMO TO: Ms. Della Hammond**

**FAX NO.: 301-827-4350**

**FROM: Yolanda Smith**

**SUBJECT: RX File (K011571)**

**No .of Pages _25__**

**Dear Ms. Hammond:**

**The following is the information provided by RX Files on software verification and validation.**

**If you have any questions, please contact me at (888) 729-9674.**

**Sincerely,**

**Yolanda Smith**

73

Testing of PC applications:

Software Validation & Verification (b) (4)

[redacted]

Testing of Palm Applications:

Software Validation & Verification (b) (4)

[redacted]

74

Software Validation & Verification (b) (4)

[redacted]

Software Validation & Verification (b) (4)

[redacted]

Software Validation & Verification (b) (4)

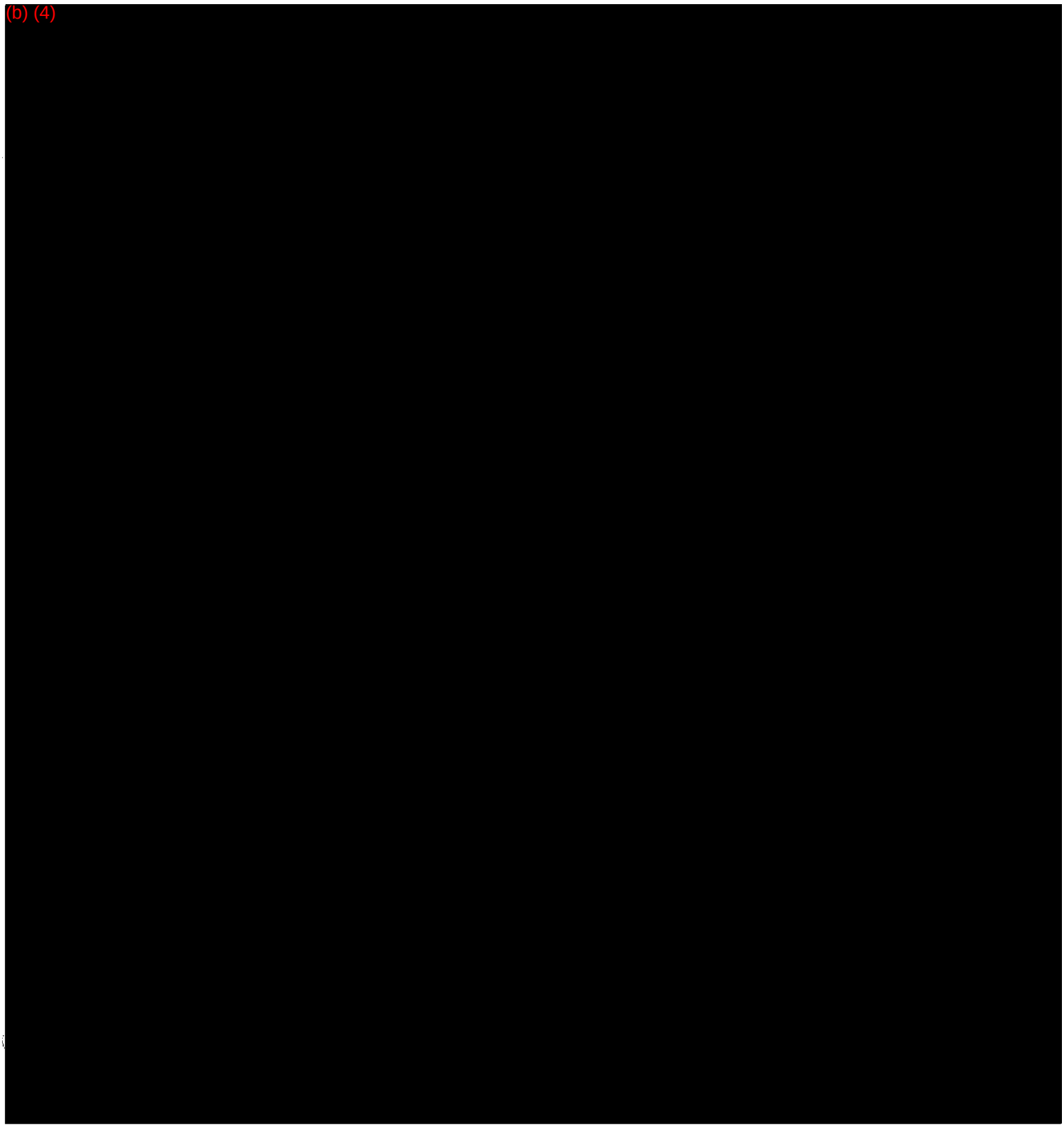
[redacted]

Software Validation & Verification (b) (4)

[redacted]

# System Context Diagram, Continued

(b) (4)



(b) (4)

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# Activity Requirements - Evaluate Special Needs and Quantities, Continued

(b) (4)

[redacted]

## Activity Requirements - Evaluate Special Needs and Quantities, Continued

(b) (4)

[redacted]

# Activity Requirements - Evaluate Special Needs and Quantities, Continued

(b) (4)

[redacted]

# Activity Requirements - Evaluate Special Needs and Quantities Continued

(b) (4)

[redacted]

# Activity Requirements - Evaluate Special Needs and Quantities, Continued

(b) (4)

[redacted]

# TRxF Clinical IDS Evaluation Procedure

(b) (4)

[redacted]

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(b) (4)

[redacted]

(b) (4)

[redacted]

# Smith Associates

P.O.. Box 4341 Crofton MD, 21114
Tel: (410)451-0639 Fax: 410(793-0448
E mail: YSmith9746@aol.com
Website: fdaconsultants.com


# FAX

**DATE: July 23, 2001**

**MEMO TO: Ms. Della Hammond**

**FAX NO.: 301-827-4350**

**FROM: Yolanda Smith**

**SUBJECT: RX Files (K011571)**

**No .of Pages _7__**

**Dear Ms Hammond:**

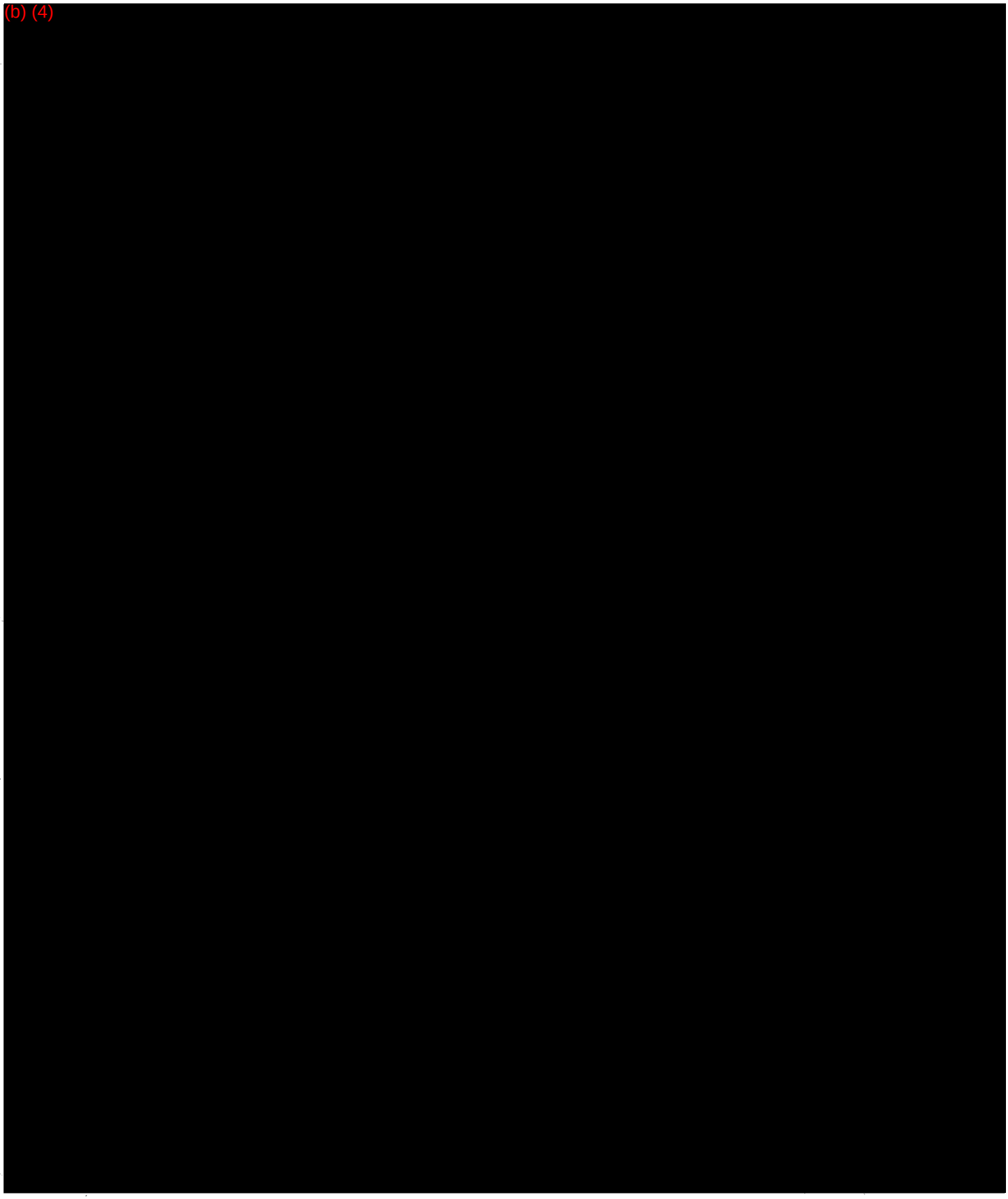
**The following is the second half of the information provided by RX Files on the software verification and validation.**

**If you have any questions, please contact me at (888) 729-9674.**

**Sincerely,**

**Yolanda Smith**

(b) (4)



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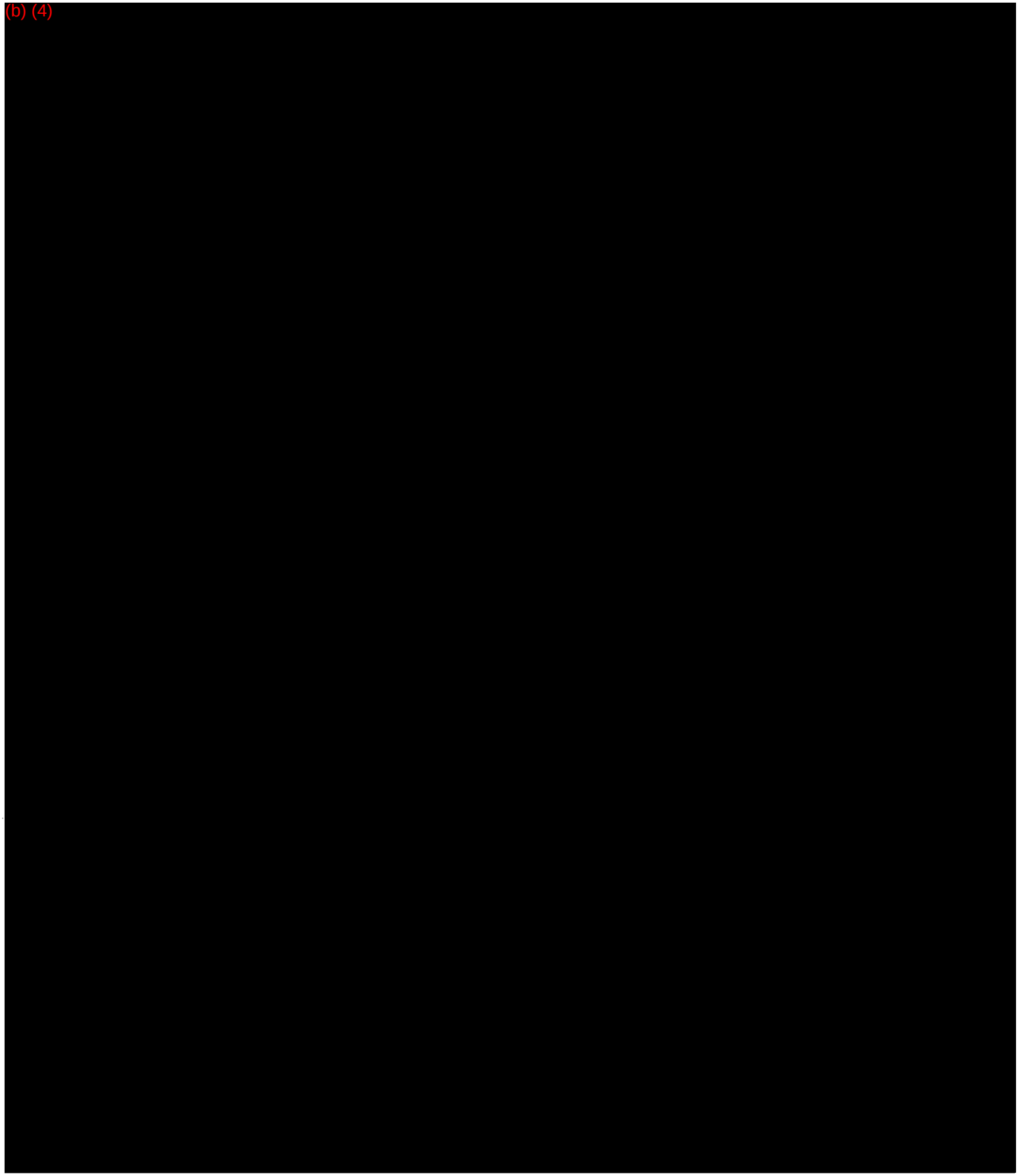
(b) (4)



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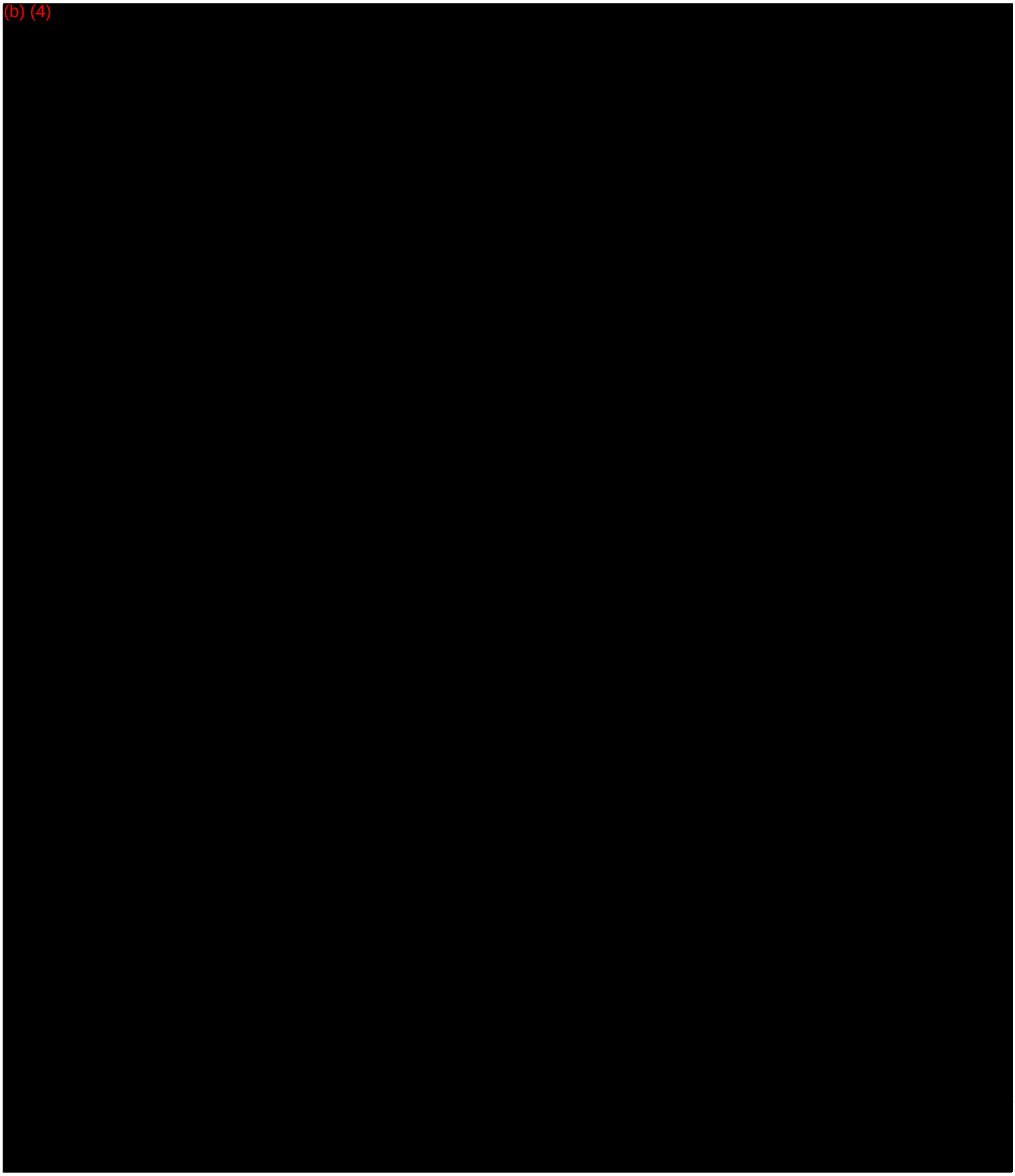

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[redacted]

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 21, 2001

THE RX FILES CORPORATION
C/O SMITH ASSOCIATES
P.O. BOX 4341
CROFTON, MD 21114
ATTN: YOLANDA SMITH

510(k) Number: K011571
Received: 21-MAY-2001
Product: TRXF INTELLIGENT DOSING SYSTEM (IDS) -DOSING CALCULATOR SUITE

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification 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.

On January 1, 1996, FDA began requiring that all 510(k) submitters provide on a separate page and clearly marked "Indication For Use" the indication for use of their device. If you have not included this information on a separate page in your submission, please complete the attached and amend your 510(k) as soon as possible. Also if you have not included your 510(k) Summary or 510(k) Statement, or your Truthful and Accurate Statement, please do so as soon as possible. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers Assistance (DSMA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the Document Mail Center will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations, we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official. Any telefaxed material must be followed by a hard copy to the Document Mail Center (HFZ-401).

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff

K011571

# RxFiles Intelligent Dosing System 510(k)

AN
7

104

 K011571

**RxFiles Corporation 342 Tamiami Trail South Nokomis, FL 34275**

May 11, 2001

Food and Drug Administration
Office of Medical Devices
Document Control Center
9200 Corporate Blvd.
Rockville, MD 20850

Attention: Document Mail Clerk

This is to notify you of the intention by The RxFiles Corporation to manufacture and market the following device.

| | |
|---|---|
| **Classification Name:** | Calculator, Drug Dose |
| **Common/Usual Name:** | Dose Calculator |
| **Proprietary Name:** | TRxF Intelligent Dosing System™ (IDS™) –Dosing Calculator Suite |
| **Establishment Registration Number:** | |
| **Classification:** | NDC |
| **Classification Panel:** | 868.1890 |

**Labeling/Product Information/Promotional Material:**

| | |
|---|---|
| **Indications for Use, Product Description:** | Reference Section 1 |
| **Labeling: User Manual (Help Files) Website and Product Literature:** | Reference Section 2 |
| **Equation Formula:** | Reference Section 3 |
| **Hazard Analysis** | Reference Section 4 |
| **Software Requirement Specifications:** | Reference Section 5 |
| **Design Specifications:** | Reference Section 6 |



AM

**Architecture Design Charts:** Reference Section 7

**Software Traceability Matrix:** Reference Section 8

**Risk Management Activities:** Reference Section 9

**Comparison of Predicate Devices:** Reference Appendix 10

| ***Company*** | ***Product*** | ***510(k)#*** |
|---|---|---|
| RetinaLabs.com | PDT DoseCalculator | K0000418 |

Mrs. Yolanda Smith –consultant-of Smith Associates is authorized to represent The RxFiles Corporation. in connection with this notification. Her contact details are as follows:

Smith Associates
PO Box 4341
Crofton, Maryland, 21114
Tel: (410)-451-0639
Fax: (410)-793-0448

Please contact Mrs. Smith with regard to any additional information that may be required.

Sincerely,

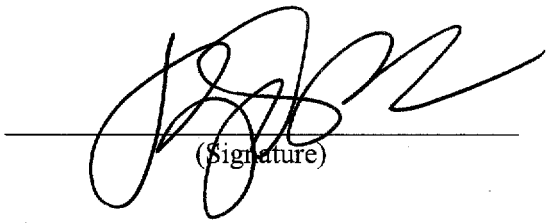
Yolanda Smith
E .J Smith
Christina Smith

**Appended Statements:**

Indications for Use Form: 21CFR801.109
Premarket Notification 510(k) Statement
Premarket Notification Truthful and Accurate Statement

# PREMARKET NOTIFICATION
# TRUTHFUL AND ACCURATE STATEMENT
# [As required by 21 CFR 807.81 (j)]

I certify that as Director of Regulatory Affairs for The RxFiles Corporation , 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.



(Signature)

JOHN D. KUTZKO

(Typed Name)

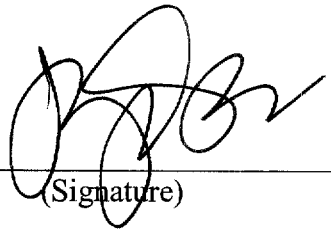
MAY 10, 2001

(Date)

(Premarket Notification 510(k) Number)

# PREMARKET NOTIFICATION
# 510(K) STATEMENT
# (As required by 21 CFR 807.81)

I certify that, as Director of Regulatory Affairs for The RxFiles Corporation, I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secrets and confidential commercial information, as defined in 21 CFR 20.61



(Signature)

(Typed Name)

(Date)

(Premarket Notification 510(k) Number)

**510(k) Number (if known):**

**Device Name**: TRxF Intelligent Dosing System™

**Classification Panel**: 868.1890

**Indications for Use:**
The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx™, InterchangeRx™ and PracticePrescribeRx™. The DoseRx™ is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRx™ is designed to switch a patient from one brand of agent to another while maintaining the therapeutic effect of the original agent. The PracticePrescirbeRx is a dosing simulator that offers graded prescriber training of next dose calculation scenarios with scalable patient response and surrogate marker inputs that allows the healthcare provider to gain guided and measured experience in calculating the next dose for a new or infrequently used drug.

The IDS™ is not a substitute for clinical reasoning. The IDS™ is an aid for trained clinicians based upon significant and properly entered data. Final drug dose recommendations for a patient must be made only after careful consideration of the full clinical status of the patient. No medical decision should be based solely upon the results provided by this software program.

**(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)**
**Concurrence of CDRH, Office of Device Evaluation (ODE)**

**Prescription Use**_____ **or** **Over the Counter Use**_____

# TABLE OF CONTENTS

# GLOSSARY OF TERMS

| | |
|---|---|
| **Adverse Drug Events (ADEs)** | Adverse Drug Events occur when patients receive either to high a dose for their system, too low a dose, the wrong medication, or they simply experience an allergic reaction. Non-serious ADEs would be headaches or dry mouth, serious ADEs could include seizure, stroke or heart attacks. |
| **AI Artificial Intelligence** | Any computer program or software that is designed to perform a function, but that cannot produce ideas or solution: with out input. |
| **Algorithm** | A predetermined set of instructions for solving a specific problem in a limited number of steps. |
| **Anthropometry** | Method of measuring body fat by pinching key points (back, hips, upper arm); not considered highly accurate. |
| **Anticoagulant** | Agents that thin the blood, frequently prescribed for heart attack and stroke victims. |
| **Antidiabetic** | An agent that prevents or alleviates diabetes. For example Insulin. |
| **BCA, Body Composition Analyzer™** | RxFiles.Net-owned BCA tool. "BCA" is also protected. US patent #5,372,141. Includes 58 patent claims. "Appara and software to establish and assessment of body composition and an initial and ongoing dataset of tissue and fluic volumes." |
| **BIA** | Bioelectrical Impedance Analysis |
| **BIS** | Bioelectrical Impedance Spectroscopy |
| **CPT** | Common Procedural Terminology (Codes are referenced from the American Medical Associations handbook, Comn Procedural Terminology CPT 2000, 4th edition.) |
| **DRx, DoseRx™** | (Patent Pending 7/14/00) Software products to provide proscribing recommendations. This is part of the IDS™ prod offering. |
| **ECW** | ExtraCelluair Water |
| **Efficacy** | The more positive aspect of an agent or drug, meaning that the drug is being effective and therapeutic. |
| **EI, EI-I-AID, ENHANCED INTELLIGENCE™** | (Patent Pending 7/14/00) "Unspecified Medical Related Services." Refers to the 'artificially intelligent' brain of the II software. |
| **EI-BCA™** | (TM Pending) "Software products for medical related services, namely, pharmaceutical services." |
| **EI-INSULIN™** | (TM Pending) "Software products for medical related services, namely, pharmaceutical services." |
| **EI-WARFARIN™** | (TM Pending) "Software products for medical related services, namely, pharmaceutical services." |
| **FPL** | Final Printed Labeling |
| **GENERATION Rx™** | (Patent Pending 7/14/00) "Software products to calculate the next best drug dose, and medical diagnostic instrumen |
| **ICW** | IntraCelluar Water |
| **IDS, Intelligent Dosing System™** | RxFiles.Net-owned tool. 1. (Patent Pending 7/14/00) "Software products to calculate the next best dose." ALSO: 2. (Patent Pending 7/14/00. Will include 15 patent claims.) "Method and system for use in treating a patient with any drug to optimize therapy and prevent an adverse drug response." |
| **Impedance Plethysmography** | Recording changes in electrical impedance between electrodes placed on opposite sides of part of the body as a measure of volume changes in the path of the current. |
| **IND** | Investigational New Drug |
| **INR** | International Normalized Ratios |
| **IRx, InterchangeRx™** | (Patent Pending 7/14/00) "Software products used to change a prescription drug from one brand to another or to a generic." |
| **NDA** | New Drug Application |
| **Non-Parametric Calculator** | Part of the DoseRx software for subjective surrogate markers, or clinical impressions. |
| **Parametric Calculator** | Part of the DoseRx software for objective surrogate markers. |
| **phar·ma·co·dy·nam·ics** | That branch of pharmacology which considers the mode of action, and the effects, of medicines. |
| **phar·ma·co·ki·net·ics** | 1. The process by which a drug is absorbed, distributed, metabolized and eliminated by the body.2. The study of th process. |

| | |
|---|---|
| **Phase 0 Safety** | Pre-clinical testing of several dosages over relevant time periods on at least two species |
| **Phase 1 Clinical Trials** | Small doses on healthy volunteers: pharmacokinetics and side effects |
| **Phase 2 Clinical Trials** | Small sample of hospital patients |
| **Phase 3 Clinical Trials** | Broader clinical trials on patients |
| **Phase 4 Clinical Trials** | Post-approval, Post-marketing Trials called for by a) Drug Company b) The FDA or c) Third Party. Answers new questions not answered in Phases 1-3. Trials could occur directly following approval, or years after and could last fr a few weeks to several years. Potentially expands indications for which drug can be prescribed, and therefore, expands patient population. |
| **Plethysmography** | The gathering of physical data pertaining to organ, limb, fat and or hydration composition. |
| **PRACTICE PRESCRIBERx™** | (Patent Pending 7/14/00) "Software products to provide prescribing simulations." This is part of the IDS product offering. |
| **RC3T, Random Concentration controlled clinical trials(SM)** | (SM Pending 7/14/00) "Unspecified medical related services." |
| **Surrogate Marker** | Any affect a drug would cause on a patient OR any measurable response used to illustrate progress towards an outcome or endpoint. For our purposes, specifically affected by agent, post-agent. Can't be isolated: must be seria looked at again and again. |
| **TBW** | Total Body Water |
| **Toxic Toxicity** | A reference to the negative aspects of certain drugs, for instance chemotherapeutics which can cause nausea, or immunosuppressants that can cause liver damage. These are highly toxic drugs that prescribers need to dose cautiously to prevent the patient from reaching to high a level of toxicity, which could lead to an adverse event. |

# SECTION 1
# INDICATIONS FOR USE, BACKGROUND, SOFTWARE DESCRIPTION

# SECTION 1: INDICATIONS FOR USE, BACKGROUND, SOFTWARE DESCRIPTION

## 1.0 Intended Use:

The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx™, InterchangeRx™ and PracticePrescribeRx™. The DoseRx™ is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRx™ is designed to switch a patient from one brand of agent to another while maintaining the therapeutic effect of the original agent. The PracticePrescirbeRx is a dosing simulator that offers graded prescriber training of next dose calculation scenarios with scalable patient response and surrogate marker inputs that allows the healthcare provider to gain guided and measured experience in calculating the next dose for a new or infrequently used drug.

The IDS™ is not a substitute for clinical reasoning. The IDS™ is an aid for trained clinicians based upon significant and properly entered data. Final drug dose recommendations for a patient must be made only after careful consideration of the full clinical status of the patient. No medical decision should be based solely upon the results provided by this software program.

## 1.1 Background of Current Dosing Methods:

How does a prescirber know how much of a drug to prescribe?

Ultimately, the only true answer to this question is that the prescriber can't know what amount of any given drug to prescribe for any given patient initially. We do have Population Models that map certain observations in a generic way, indicating for instance that young adults tolerate certain agents better than the elderly, or that members of certain races respond differently than the members of others. However, patients with no history of having been exposed to certain agents offer no assurance that their genetic make-up sill allow then to respond normally, or within some sort of average range. This could mean that one patient may have no response whatsoever to a given agent, while on the other end of the spectrum, another patient may experience a rapid therapeutic response, or anaphylactic shock. Beyond a hope and a guess, the following explanations represent the greater portion of medications dosing methods.

**Population Pharmacokinetics**
The study of the sources and correlated of the variability in plasma drug concentrations between individuals representative of those in whom the drug will be used clinically when relevant dosage regimens are administered. Population pharmacokinectics seeks to discover which measureable pathophysiologic factors cause changes in the dose-concentration relationship, and to what degree so that the appropriated dosage can be recommended. Doses determined, and administered are generally doses deemed appropriate for populations based on age, weight, gender, height, and disease state.

**Clinical Pharmacokinetics**
This model attempts to provide both a more quantitative relationship between dose and effect, and the framework with which to interpret the measurements of concentration of drugs in biological fluids. The most important principles fundamental to the interpretation of these

measurements are Clearance, Volume of Distribution, and Bioavailability. The importance of clinical pharmacokinetics in patient care rests on the improvement in efficacy that can be attained by attention to its priniciples when dosage regimens are chosen and modified.

Therapeutic Drug Monitoring, synonymous with Clinical Pharmacokinetics, and other dosing models, is the generic term that reflects the major use of measured concentrations (markers) of drugs at steady state to quantify the estimate of the effect of bioavailablity (F) on clearance (CL). This is thence used to design a dosing regiment to target.

**Pharmacodynamic Dosing**
Simply put, pharmacodynaics is what drugs do to the body. Technically, it is the study of the biochemical and physiological effects of drugs and their mechanisms of action.
Pharmacodynamic dosing provides the tool to characterize the full sequence and scope of actions of each drug. Considerable inter-individual variation in response to drugs remains after the concentration of the drug in plasma has been adjusted to a target value; for some drugs, this pharmacodynamic variability accounts for much of the total variation in responsiveness among patients. The relationship between the concentration (marker) of a drug and the magnitude of the response may be complex, and cannot be predicted using pharmacokinetic principles.

**Skin Surface Area Dosing:**
Many cancer drugs are toxic and range and the range between maximum benefit and sever side effects is narrow. So doses are adjusted for the size of your body. To do this there needs to be a measurement of "the amount of the Patient." Then a dose can be given as amount of drug per amount of the patient's "space of occupation." There are two basic ways this is done. The obvious simple way is to simply weigh the patient in Kilograms. In this case, the amount of a dose will be given in Milligrams of Drug per Kilogram of body weight, abbreviated mg/kg (Or International Units of Drug per Kilogram of body weight, abbreviated IU/kg).

Oncologists sometimes use a more complicated way of measuring body size, or Body Surface Area (BSA). BSA is measured in square meters, abbreviated $m^2$. This is to compensate for the fact that people, particularly people with cancer, may be underweight or overweight and the idea would be to give them an amount of drug that would be appropriate for what their size *should be*, disregarding how much fat and muscle they have.

**Bayesian Pharmocokinetics Dosing:**
The Bayesian theorem deals with probabilities. What is the probability of getting a therapeutic response from a particular dose? The Bayesian approach is subjective, and requires assessing prior probabilities. This requirement forces users to relate current experimental evidence to other available information – including previous experiments of a related nature, where "related" is judged subjectively. For drug dosing, it uses the "prior" information about the drug and various responses (concentration) from a known population to develop statistical confidence for predicting dosages.

## 1.2 Product Description:

Intelligent Dosing System™
The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx™, a "next" dose calculator, InterchangeRx™, a therapeutic interchanger to switch a patient from one agent, brand or class of drug to another, and Practice PrescribeRx™, a graded prescriber training

simulator for new or infrequently used drugs. The IDS™ is based on a precursor of Enhanced Intelligence™ from an Expert Computer System featuring an artificially intelligent modeling system™ (AIMS™). The AIMS™ contains a decision matrix and an inference engine encompassed in a designer equation. The equation holds true for all drugs.

All IDS™ products and software can be accessed with Palm Pilot®, Windows, or Windows CE® Operating Systems

**DoseRx™**

The comprehensive database necessary for the expert environment in our DoseRx™ includes all available information about the subject drug as well as what steady and dynamic state dose is to surrogate marker (concentration) values, and patient findings. A designer equation is then applied with numerical values based on the following parameters: the amount of the subject's last dose, the surrogate marker (SM) response, the current dose, and the desired SM response. The SM can be determined and changed as necessary by the healthcare provider, and can be objective or subjective, positive or negative, based upon the unique combination of circumstances presented by the patient's condition, disease progression, co-morbidities, compliance and therapeutic response.

By using a very brief amount of easily gathered patient information, and selecting any subjective or objective marker that is clearly affected by the drug, our DoseRx™ will achieve the healthcare provider's selected surrogate marker target value with mathematical precision. For added patient safety, attached to our equation is a "stochastic patient control loop," an open equation enabling a dose adjustment up or down in relation to a second marker to accommodate any vagary or random event. Our system provides a standardized, auditable and measurable means to optimize dose calculations. The technique provides the means for rapid, effective titration, and optimal pharmacologic intervention.

**InterchangeRx™**

The InterchangeRx™ software eliminates the concern and emphasis placed on brands or agents being bioequivalent with respect to prescribability and switchability. As bioequivalence is no guarantee of equal therapeutic effect, the InterchangeRx™ method utilizes our Enhanced Intelligence℠ technology to leapfrog to the desired therapeutic effect of the new agent, and calculates whatever dose of the drug is necessary to maintain the established therapeutic effect of the previously used brand or agent. This unique and novel software may also be used if a prescriber desires to change a patient from an agent belonging in one drug class to another agent in a second class while maintaining a level of pharmacologic therapeutic efficacy. This may require monitoring more than one surrogate marker, that may be of either efficacy or toxicity, or both, as long as they are specifically and serially impacted by either one or both of the agents involved in the switch. The ability to utilize additional markers when changing from one pharmacologic class to another in order to maintain or improve upon an established level of therapy is a unique and valuable characteristic of InterchangeRx™.

**Practice PrescriberRx™**

This program provides graded prescriber training through a computerized simulation of endless "next dose calculation" scenarios, with scalable patient response and surrogate marker inputs. The Practice PrescriberRx™ allows healthcare providers to gain guided and measured experience in calculating the next dose for a new or infrequently used drug. Each simulated experience is

graded as compared to the computer, with a cumulative score maintained, so the "student" can self-monitor progress until able to demonstrate a specific or required level of expertise. Unique parameters such as specific disease state, desired treatment outcome, individualized response and compliance level, are all documented for the user. Through this simulation the healthcare provider is educated to the drugs parameters and the appropriate surrogate markers, in relation to both patient and disease, rendering this a thoroughly comprehensive educational experience.

### 1.3 Device Features controlled by Software:

The IDS controls no device or features thereof. The only function the user of the IDS can control or modify are drug selection (by name) and input parameter (doses and level or response markers) that are entered into an equation the system makes use of, this equation cannot be changed. After selecting a drug, the user enters previous and current dose and level or surrogate marker information as well as desired level or surrogate marker information about a patient. These parameter are then entered into the equation to calculate the next dose

### 1.4 Operational Environment:

**Program Language:** Microsoft Visual Basic 6.0

**Hardware Platform:** IBM compatible PC's using Windows or Win CE and Hand held devices such as Palm Pilot, Cassiopeia & Jordonna

**Database:** MS Access 2000

### 1.5 Practical Applications

The end user of the IDS™ is the prescribing clinician. The following are some of the practical applications:

1. Randomized Concentration Controlled Clinical Trials ($RC^3T$'s)™

The application of the IDS™ software to the process of drug development vastly increases the speed and efficiency in all phases of clinical trials. Placebo control trials become unnecessary and all volunteers for these trials receive treatment. Applying the IDS™ method provides a simple, effective, and economical means to establish and maintain the optimal therapeutic dose and resultant desired effect. After the IDS™ has stabilized all enrollees into the initial "low" stage group, all subjects are evenly divided and randomly assigned to low, medium, and high dose groups. Each level is then monitored, and subjects are moved as necessary into their respective, or optimal, levels of concentration. If a subject "fails" a level, s/he is rapidly moved (titrated) to the next level, up or down, and re-evaluated. The end-result is a more humane, effective, and informative trial, establishing not only efficacy, but also the optimal dose for specific subject and disease characteristics. There is no reason why this method should not be the new "Gold-Standard."

2. Xeno Drug Development

As with the RC$^3$T's™, using the IDS™ drug dosing methodology provides a unique opportunity to initiate drug development in other species. The dose response relationship can be illustrated by our three-dimensional mapping technique to facilitate the initial understanding of the drugs effect. Through this illustration, both the potential and severity of adverse events can be better controlled and/or avoided. Here again the IDS™ provides the means to establish the most safe and effective dose through rapid titration in RC$^3$T'™ type testing. Because the IDS™ is accurate with all species use at this level is not only possible, but logical and humane as well.

3. Xeno Transplantation

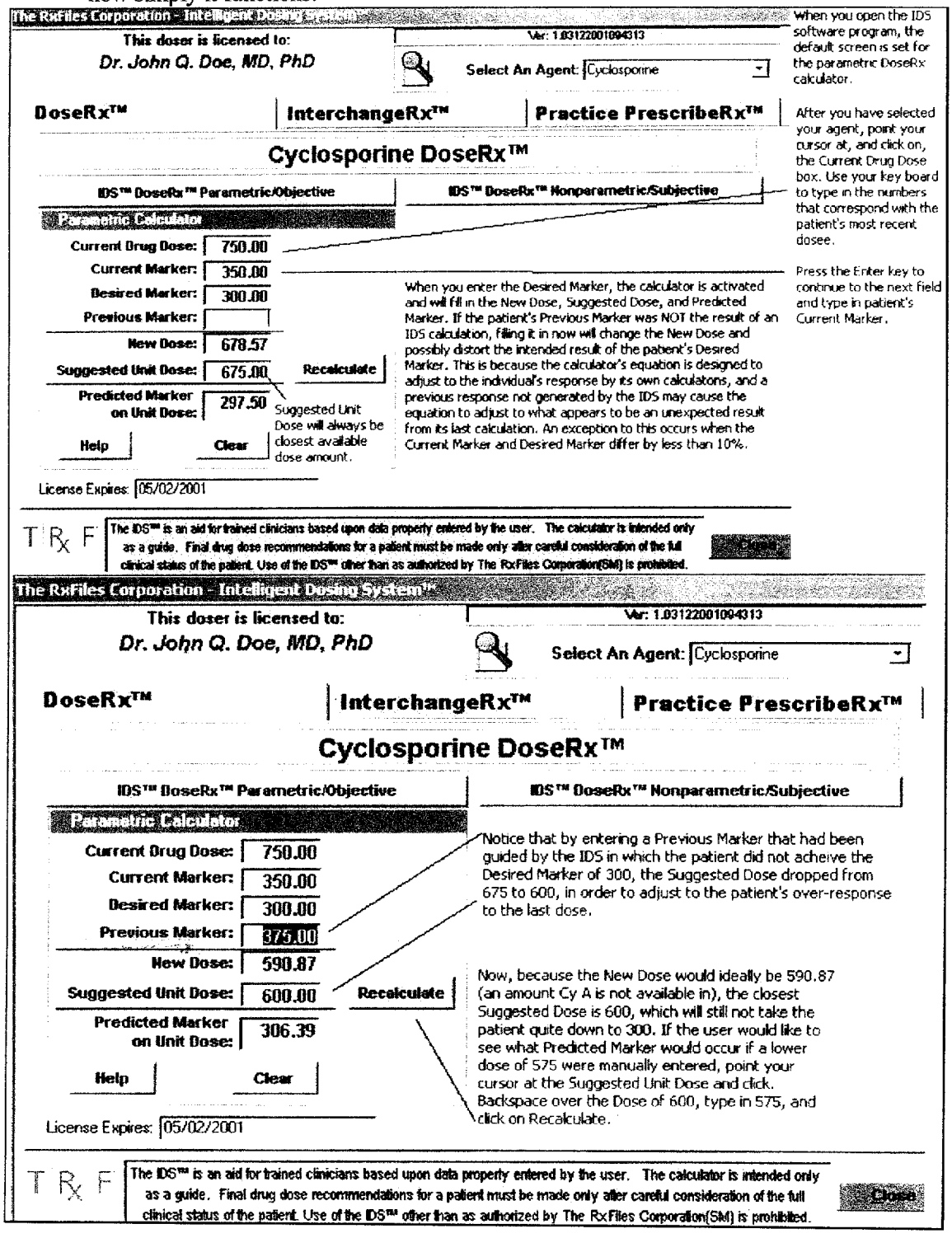
In earlier development, a precursor of the IDS™ was used to manage immunosuppressants in the human recipient of a Baboon liver. Even the earlier system provided the patient with an optimal therapeutic effect without any associated adverse events throughout the remainder of his life. While xeno transplantation remains a controversial procedure, and presents an ethical and moral dilemma to which there is not currently a generally accepted solution, it is important to know what options may be effectively managed. This knowledge may, in fact eventually assist in the decision process.

4. Mapping the Surface Response Curve for Additional Drugs

Requirements for Mapping the Dose Response Curve of any class drug or agent should include at least 36 observations that track the four specific parameters last dose, last response, current dose, and current response. It is better to have steady-state markers, but this is not an absolute requirement. Observations should extend from the low to the high end of the normal dosing range of the drug, and there should be at least 12 subjects observed in the low, and 12 in the high range. For most drugs the time between Current Dose and Next Dose should not exceed 30 days. Optimally, the change between Current Dose and Next Dose would be at least 10 percent.

## 1.6 Product Sample

This is what the calculator software for the IDS™ looks like, with a brief description of how simply it functions:




16

120

# SECTION 2
# LABELING

# SECTION 2: LABELING

**2.1 Instruction Manual**
Reference Exhibit 2.1: A Guide to Using the Intelligent Dosing System

**2.2 Website**
Reference Exhibit 2.2

**2.3 Product Literature**
Reference Exhibit 2.3

# EXHIBIT 2.1
# INSTRUCTION MANUAL

# A Guide to Using The Intelligent Dosing System

# IDS™

**The IDS™ is not a substitute for clinical reasoning. No medical decision should be based solely upon results provided by this software program.**

**By The RxFiles Corporation**

T | Rx | F℠

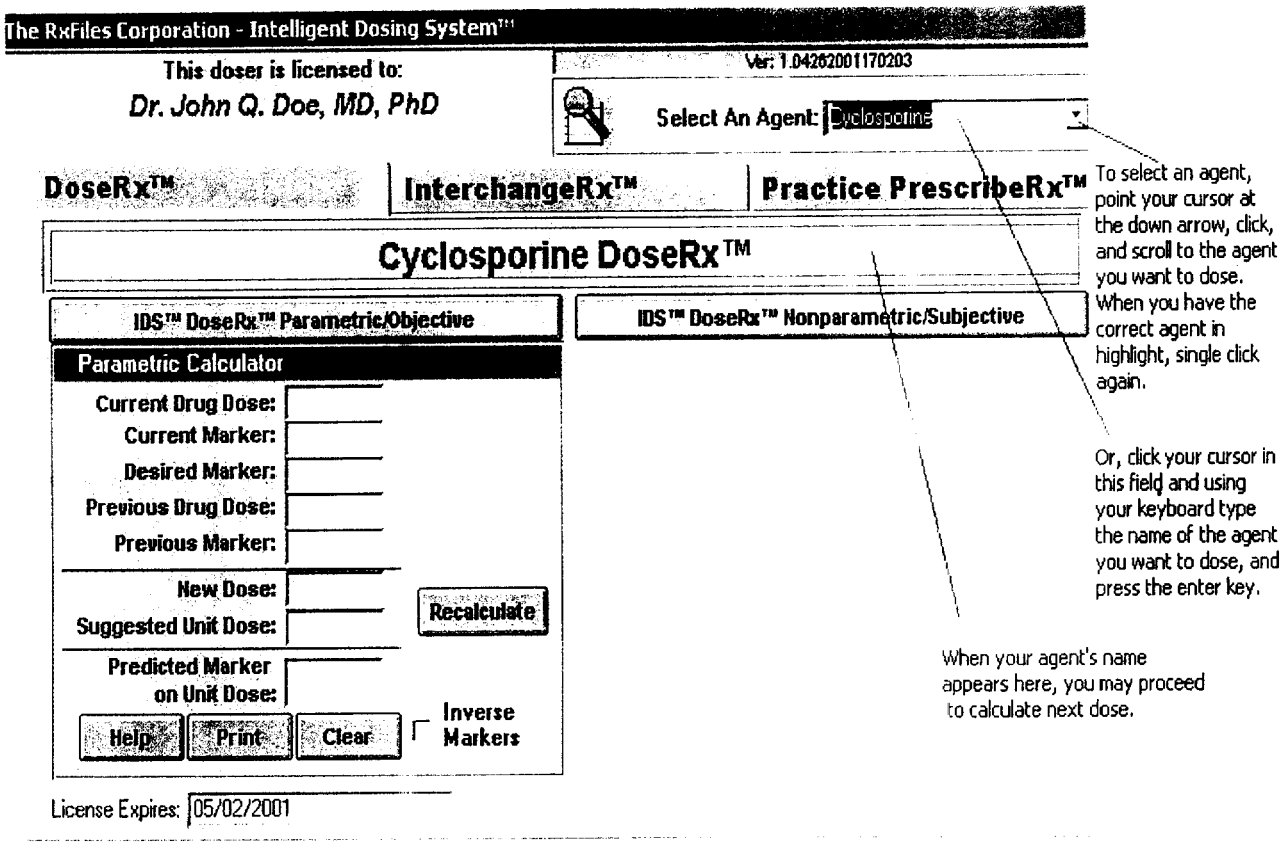
The RxFiles Corporation

# Contents

# General Information

## Selecting An Agent

To select an agent for any portion of the IDS™ software suite (DoseRx™, InterchangeRx™, or Practice PrescribeRx™) point the cursor at the down arrow box next to the "Select Your Agent" field, highlight and click on the agent you want. The default opening screen is also set for the user to simply type in the agent name using the keyboard. If typing, when the agent's name appears in selection box, press enter key. When your agents name appears on the large banner below the tabs titled DoseRx™, InterchangeRx™, and Practice PrescribeRx™ the calculator's equation is set for that agent.



# DoseRx™ In Detail

## DoseRx™ Parametric Calculator

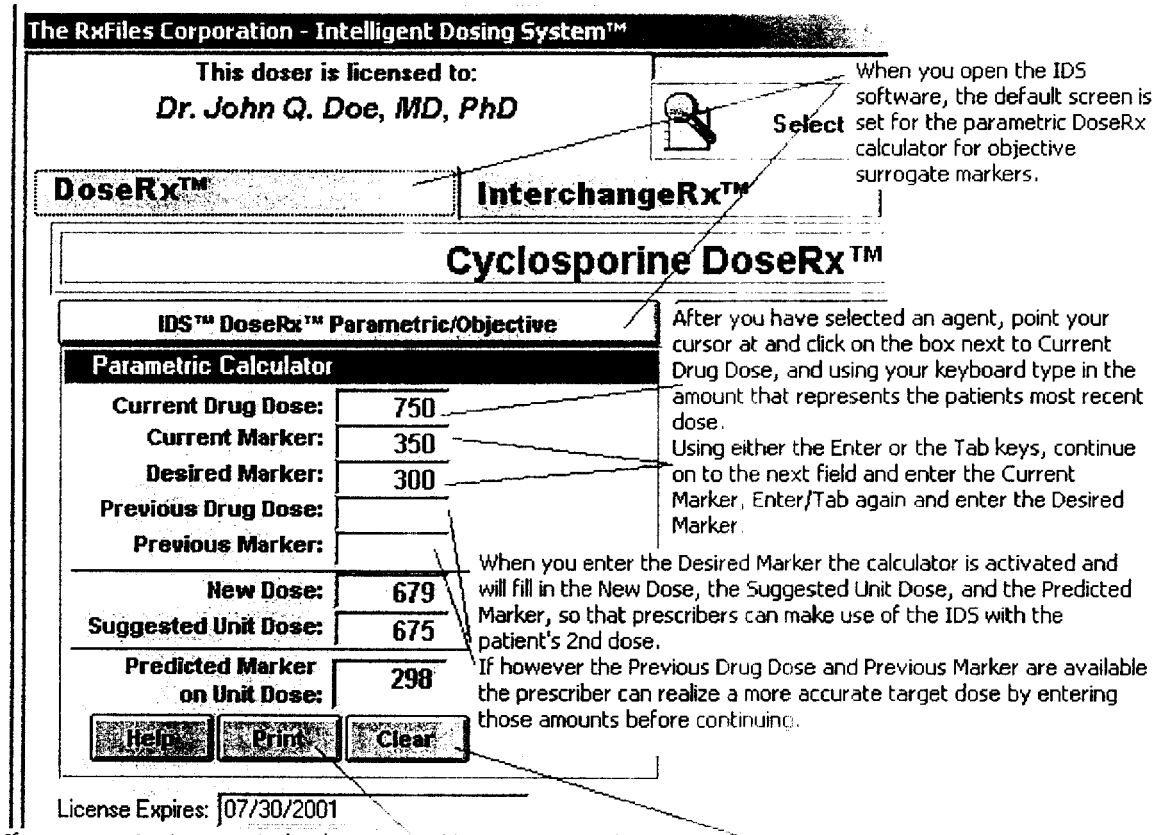
The parametric calculator is for either objective or subjective surrogate markers. The healthcare provider can select any measurable marker that is clearly being impacted by the agent(s) being dosed. Markers can denote efficacy or toxicity, and the healthcare provider can change the marker as necessary, or add markers by executing second or third calculations. However, each marker must be calculated separately.

It is important to understand that one looks at the change in response when making an observation of how the patient responded the last time through the prescribing process. Ultimately, it is what occurred ***after*** a dose that relates to where the individual currently fits on the dose-response curve. This is true whether the prescriber is dosing to a therapeutic response, or inversely, to reverse a negative response.

The IDS™ is a guiding tool; it is not a substitute for clinical reasoning. Medical decisions should not be based solely upon results provided by this software program.

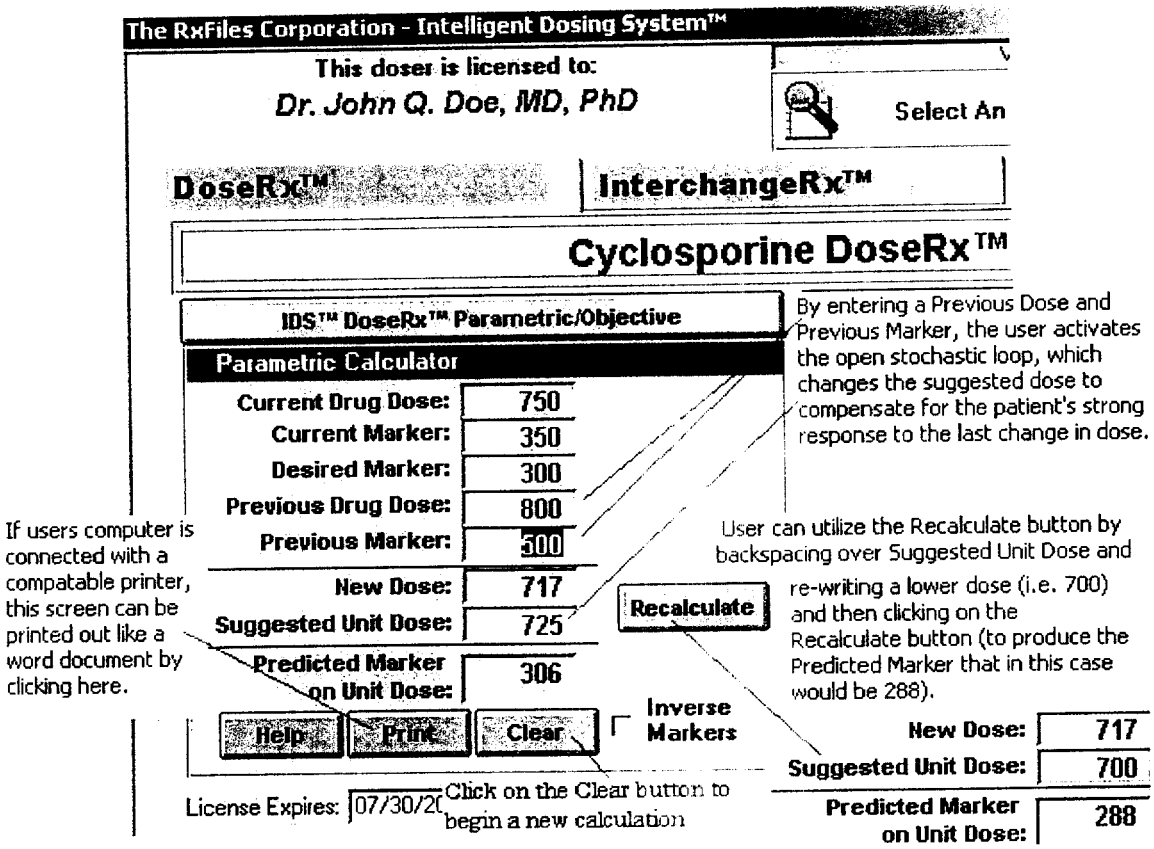
## Using the DoseRx™ Parametric

To enter the dose the patient most recently received, point your cursor at the Current Dose box and click. Using the numbers on your keyboard enter the dose. Press either the Enter or Tab key to go to next box and enter the Current Marker level representing the patient's current response. Enter or Tab again to the Desired Marker, and enter the number that represents the target marker for this patient. The calculator is always triggered at this point, and numbers will appear in the New Dose box, the Suggested Unit Dose box, and the Predicted Marker box. To complete the most accurate calculation for patients who have received two doses or more, press Enter or Tab once more and enter their Previous Drug Dose and Previous Marker; the next three fields will reconfigure appropriately.



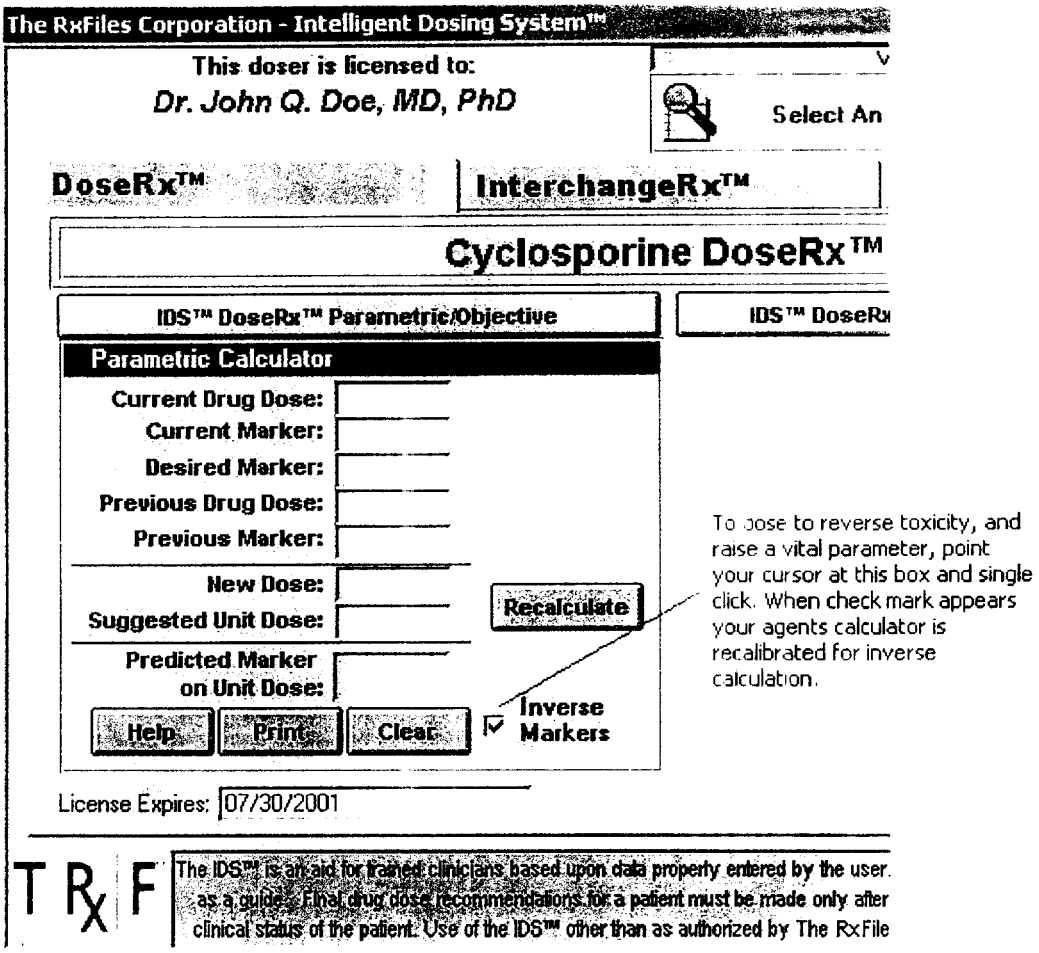
# Recalculating

Frequently the ideal dose is an unavailable amount by several decimals, this is why the nearest available amount appears in the Suggested Unit Dose box. You will notice below that box the Predicted Marker level for this patient at that dose. You can now decide if you would like to change the Suggested Dose to alter the expected outcome (for instance, if you would like to lower the dose to reduce toxicity), point your cursor at the Suggested Unit Dose box and backspace to empty that field. Use the numbers on your keyboard to enter a different dose, then point your cursor at the Recalculate button and click. NOTE: the Recalculate button is strictly for changing the Suggested Unit Dose, it is not designed to function after incorrect parameters have been entered above.



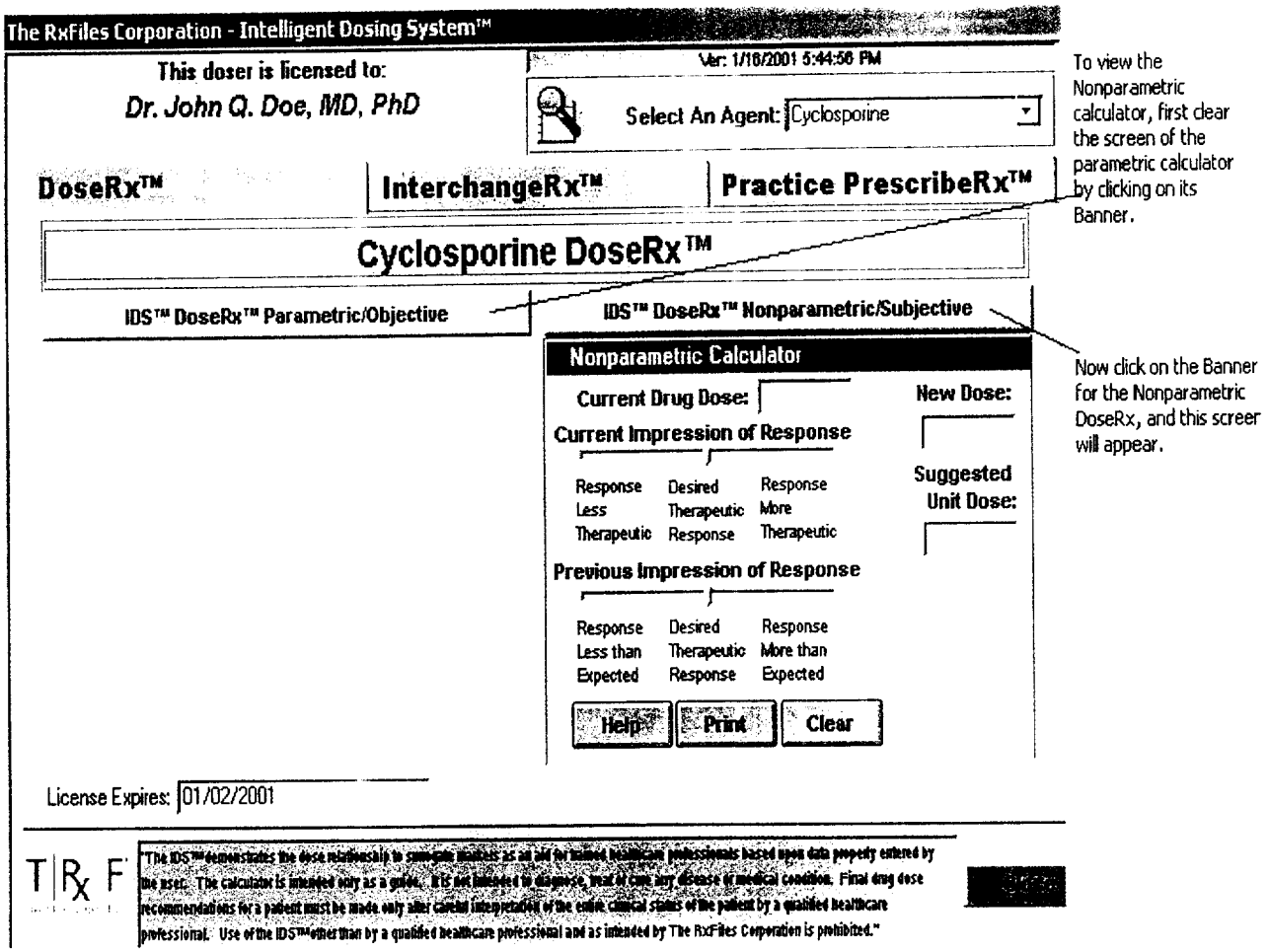

# Calculating Inverse Markers

When dosing highly toxic therapeutic agents it is often necessary to track the negative impact of the agent on the subject being dosed, and to sometimes limit dosing to reverse toxicity. In the event that an increase in dose results in the reduction of a given parameter, that parameter is known as an inverse marker. The IDS™ will calculate lower doses to raise that parameter, rather than cease dosing the patient altogether which could too greatly interrupt patient therapy. To reverse a negative impact by dosing, first select your agent and then point your cursor at the box next to Inverse Markers and click to check mark the box. This will, in essence, reverse the equation




# View DoseRx™ Nonparametric Calculator

The nonparametric calculator is for subjective surrogate markers. It is up to the prescriber to decide which agents should be dosed subjectively. In order to view and use the Nonparametric calculator simply point your cursor at the IDS™ DoseRx™ Nonparametric/Subjective box on the screen and single click. You may or may not want to close the parametric calculator while using the nonparametric function. To clear the screen, point your cursor at the IDS™ DoseRx™ Parametric/Objective box and click.




# Using DoseRx™ Nonparametric Calculator

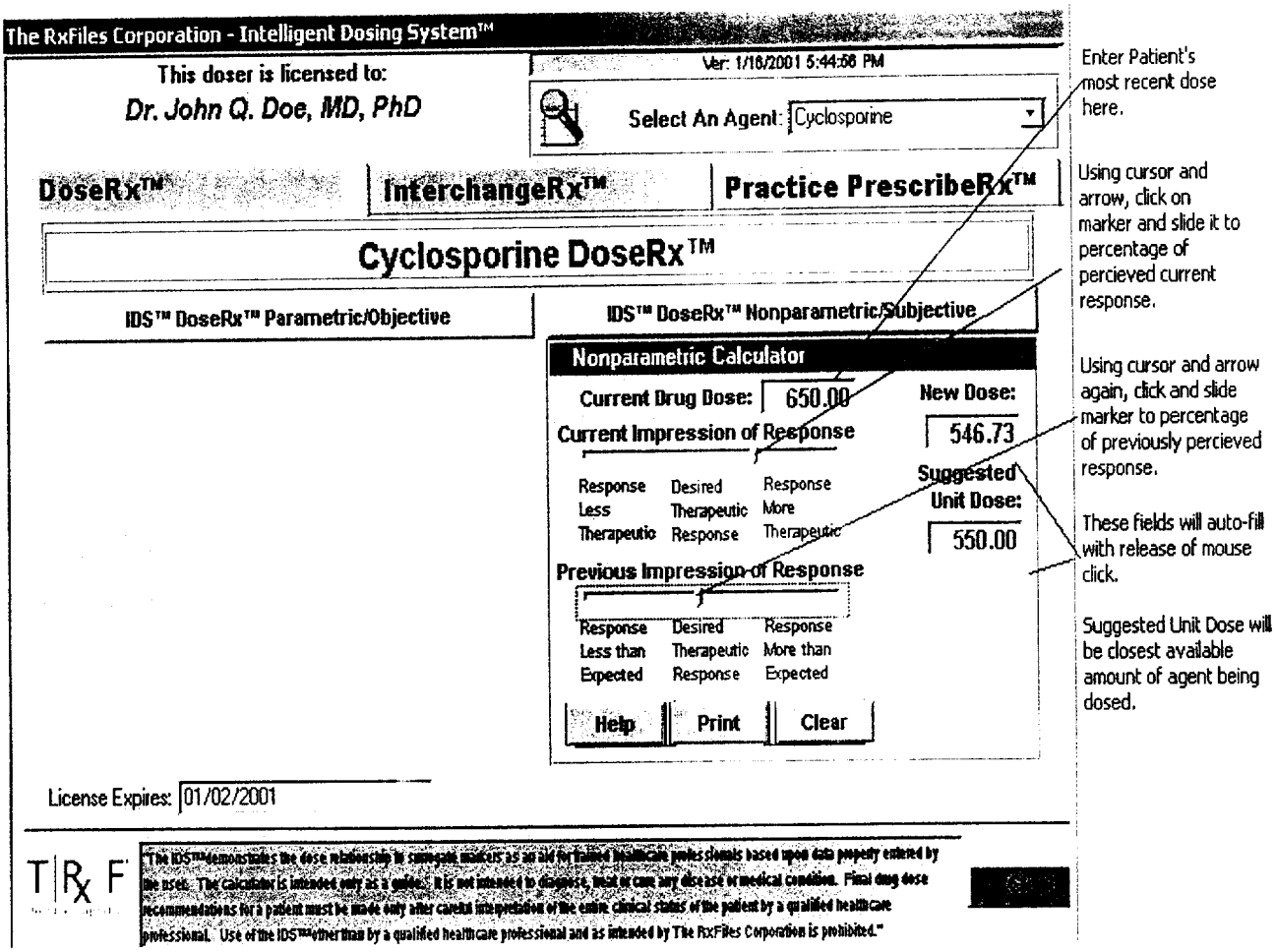
When using the nonparametric DoseRx™ the prescriber must select a subjective marker and, in on going treatment, use the same marker for serial calculations, only changing marker after two doses and a previous observation of the new marker. Prescriber may select any observable, measurable characteristic that is clearly impacted by the agent being dosed. The prescriber must then form a clinical impression as to how far off the target effect the patient is, and translate it into a percentage. Before using the scales, begin by pointing your cursor at the Current Drug Dose box, click, and using your keyboard, enter the current dose.

# Directing The Sliding Scales

At the top of this calculator is a Current Dose box to be filled in with the most recent dose the patient received. This calculator also features two sliding scale bars. Both default to 100%, which assumes that you want the patient to have a 100% response to the agent you are dosing. It is understood that patients will rarely respond in the outside (far end) ranges, for instance 10% or 190%

There are two methods of use for the scales. One way is to point your cursor at the marker in the middle of the scales, and left click on your mouse; in this way you can slide the marker to the percentage representative of first the Current Impression. You will notice that as soon as you click on the marker, a box will appear below it giving you the numeric value of its position. When satisfied with the reflection of your impression, proceed to mark your Previous Impression.

Final calculation results when you release the click on the marker. Or you may single click on the bar anywhere to the right or left of the marker to move it in 5% increments towards the cursor




# Upper Bar

The upper bar is to denote the physician's impression of how close to or far from the ideal target of 100% response that s/he deems the patient to be right now. Less than 100% means that the patient has not achieved the desired effect and that an increase in the dose will be required. Over 100% means that the patient has too much drug or is over responding, and a decrease in the dose will be reflected in the calculation.

# Lower Bar

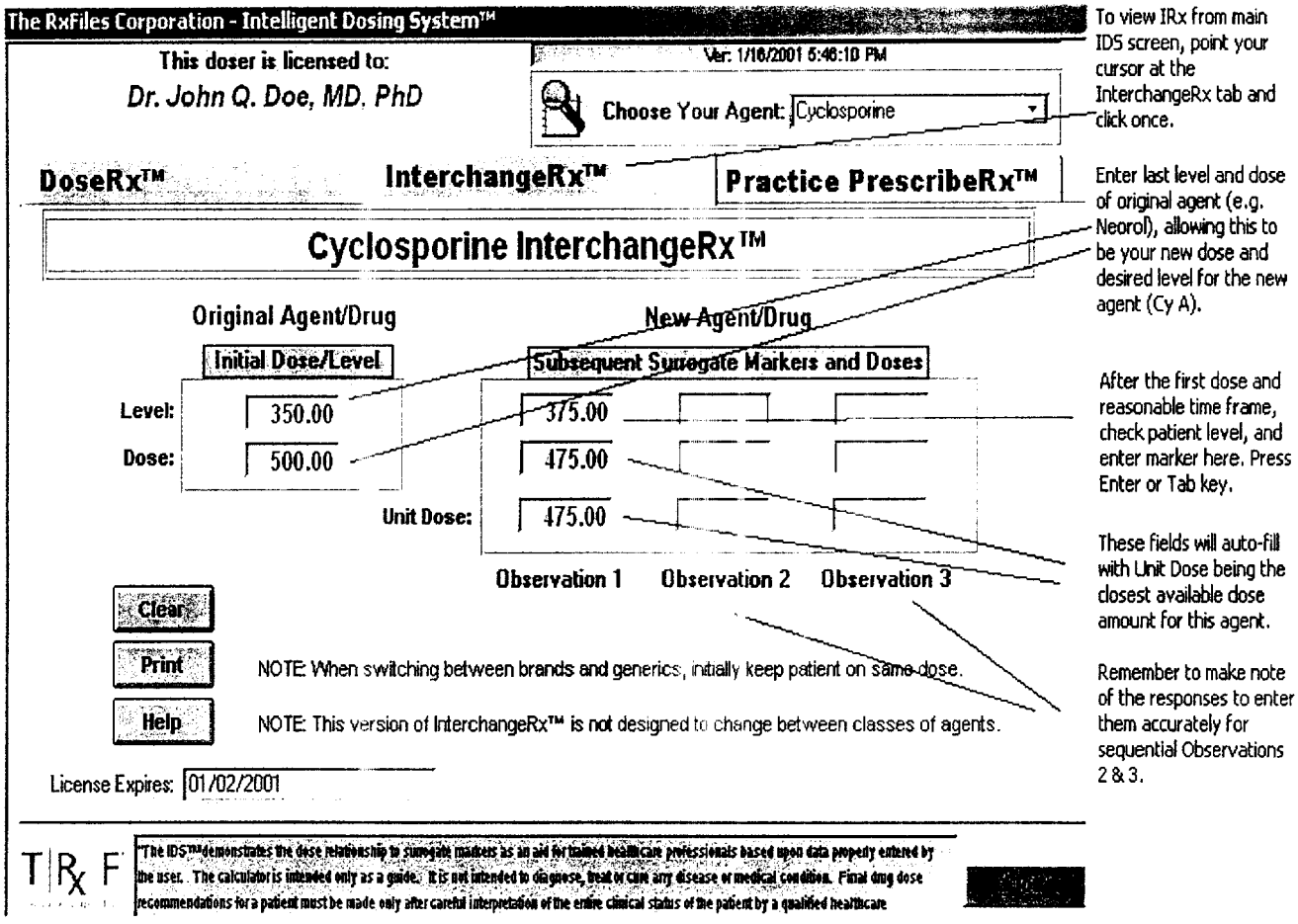
The lower bar on this screen is for the physician's impression of the patient's previous response, or, how close to or far from the target the patient was before the last dose. With the information of what dose has been administered, where the patient is now (from upper bar), and where the patient had been (this field), the calculator will fill in the new amount of dose recommended to bring the patient to 100% response. The new dose will appear when you release the mouse click on the sliding scales. Click on Print button to save a record for patient file, or to fax dose to pharmacy.

# InterchangeRx™ In Detail

The InterchangeRx™ will direct a more seamless and safe switch between similar agents for your patient without interruption of therapy. When switch is completed monitoring and accurate dosing can continue with DoseRx™.

## View InterchangeRx™ Calculator

To access InterchangeRx™ point cursor at the "InterchangeRx" bar on main IDS™ screen and single mouse click.



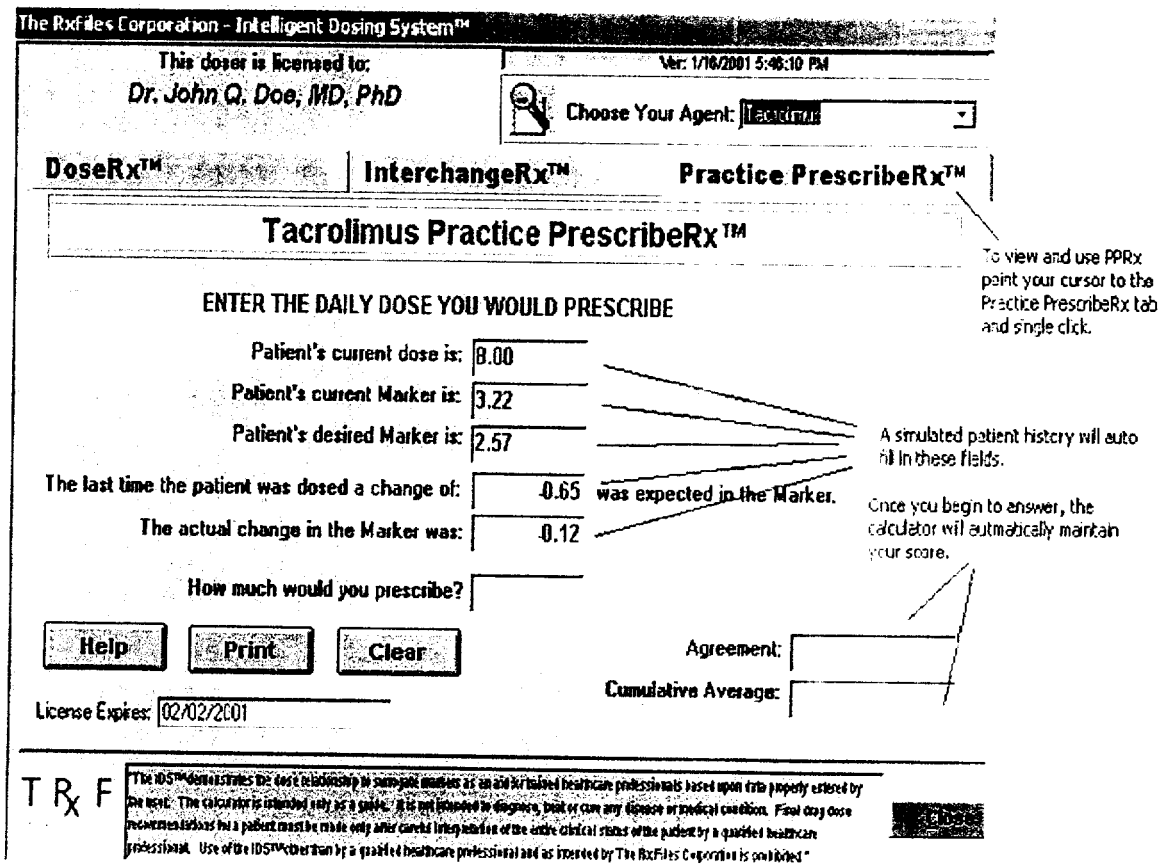
# Using InterchangeRx ™ Within Same Class

To change a patient from a Name Brand Drug to its Generic, start patient on the same dose of Generic that had been the previous dose for the Name Brand. Enter the patient's marker level at the initial dose of new agent. Keep record of each serial calculation and enter both dose and response successively for each serial dose in order to track patient response and progress. To do so, point your cursor at the Print button and single click each time you calculate. This version of InterchangeRx™ is not designed to switch patients between classes of agents.

# Practice PrescribeRx™ In Detail

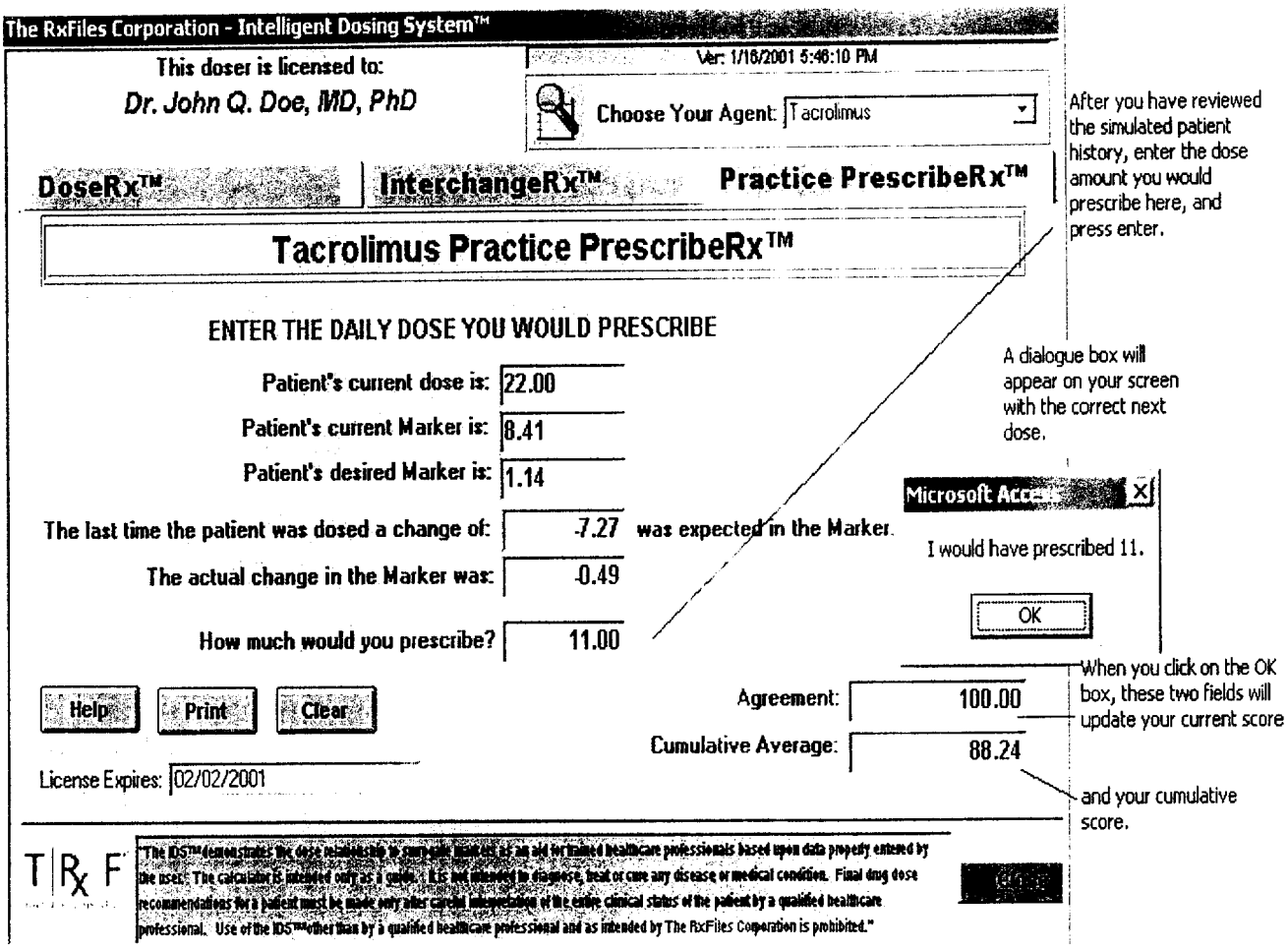
## View Practice PrescribeRx™ Calculator

To access Practice PrescribeRx™ point cursor to "Practice PrescribeRx™" tab on main IDS™ screen and single mouse click.



# Using Practice PrescribeRx™ Test

To familiarize yourself with the dose response curve of your selected agent, or to refresh your knowledge of it, begin by reading the simulated patient history provided on this screen and then, using the keyboard, enter your suggested dose where asked, "How much would you prescribe?" Press Enter key or Tab key to get PPRx™ response. A dialogue box will pop up to tell you what dose the calculator would have selected. The dialogue box will prompt you to click on an "OK" box within it; using cursor, point at the OK and click once. Both the Agreement field and the Cumulative Average field will auto-fill to inform you of your score for that particular dose, and for your running average. To begin a new dose simulation, click the Clear button. To record your score, click on the Print button



# Frequently Asked Questions

## Questions & Answers Regarding the IDS™ and Dosing

| |
|---|
| **Q. How does the IDS™ work?** |
| |
| A. The IDS™works by illustrating the dose-response curve of an agent based |
| upon three-dimensional surface mapping. The 3-D mapping results in linearity |
| factor that is integrated into a designer equation attached to a stochastic |
| patient control loop to meter the dose in response to a surrogate marker which |
| may be objective, subjective, positive or negative. |
| |
| **Q. What do you mean by surrogate markers?** |
| |
| A. A surrogate marker is any observation or measurement that can be taken from a patient that relates to the level of drug in the body, which in turn |
| relates to the efficacy or toxicity of the drug. Surrogate markers could also |
| be a physician's clinical impression, or, the result of several observations and/or measurements. This point demonstrates how the IDS™ works for and with the physician, as a tool, to improve patient dosing and care. |
| |
| **Q. Can one use various surrogate markers to dose a patient?** |
| |
| A. Yes. The 3-D mapping results in a linearity factor that is integrated into a |
| designer equation attached to a stochastic patient control loop to meter the |
| dose in response to a surrogate marker which may be objective, subjective, |
| positive or negative. This means that our discovery allows any patient to be |
| dosed on an agent based on either a positive marker such as plasma |
| concentration, blood pressure or viral load, or a negative marker of toxicity |
| such as a change in absolute neutrophil count, anemia, serum creatinine or the |
| number of episodes of diarrhea. In fact, the open loop allows for several markers to be used simultaneously, with the understanding that each one is calculated separately. |

**Q. How does the IDS™ individualize patient therapy?**

A. The IDS™ is based on the patient's previous dosing experience. It is designed to address the individual's response, and aid the physician in maintaining the optimal therapeutic effect. The plane of fit is further optimized for the individual patient by utilizing the open loop to reconfigure the plane to a three-dimensional curve.

**Q. What does the IDS™ Matrix use to dose?**

A. Archetypes of the IDS™ had the ability to use only drug blood levels, but our newest discovery, resulting in a new patent application, allows the IDS™ Matrix to dose to any surrogate marker, those that are objective or subjective, including the physician's clinical impression, and those that are indicative of therapeutic efficacy or toxicity.

**Q. Will the IDS™ Matrix replace the physician?**

A. No. The IDS™ was designed as a tool for the physician to guide drug therapy. The IDS™ simply provides a standardized "map" for the individual's expected dose to level relationship.

**Q. How is it that the IDS™ technology can predict the dose-level relationship when modern PK-PD technology cannot?**

A. Classical PK-PD methodology was designed as a descriptive science, and so it remains today. While appreciating the traditional applications of PK and PD, our technology provides the "roadmap," and therefore the opportunity, to combine technology and make a more significant improvement in-patient care. The IDS™ Matrix is predictive rather than descriptive. With this in mind, the IDS™ is better suited for patient dosing.

**Q. Should the IDS™ Matrix be used for all drugs?**

A. The best utilization of the Matrix in drug therapy comes from use with drugs that are inherently difficult to manage. Drugs with a narrow therapeutic index or range, and drugs with numerous or severe toxicities are the best candidates.

**Q. Are there populations of people that are better suited for the IDS™ Matrix?**

A. The IDS™ Matrix works and individualizes drug therapy for any population. However, children, because of their higher metabolic state require more drug for a response. Therefore, it is the pediatric population that receives the most benefit from the

| |
|---|
| Matrix, due to their being on the most non-linear portion of the plane of fit for a drug. |
| |
| |
| |
| **Q. What kind of drugs, and how many different ones can the IDS™ methodology be applied to?** |
| |
| A. In February 2000 at the CASE CDER seminar we were tasked by the FDA to apply the technology to certain therapeutic categories. Those areas included |
| Warfarin Na, Phenytoin, Digoxin, Insulin Gentamicin, Tobramycin, Vancomycin, |
| thyroid products, Chemotherapeutics, HIV Agents, Heparin, Oral Hypoglycemics, |
| Antihypertensives and the Statins. Agents we are currently working on include the Anti-depressants Prozac and Remeron, the Anti-psychotics Risperidal and Zyprexa, chemotherapeutics such as Xeloda, Taxol, Gemzar, Platinol, analgesics such as Morphine and the NSAIDS, combination Bronchodilators, Accutane, Oxygen and Potassium. |
| |
| **Q. What is the difference between parametric and non-parametric dosing with the IDS™?** |
| |
| A. Our parametric dosing system allows the input of either positive or |
| negative objective markers. Additionally, our designer equation allows us |
| to dose a patient non-parametrically such that a sliding scale allows the |
| prescriber to enter the prescriber's subjective evaluation with regard to how the prescriber would gauge the patient's last change in response, as a percentage of what was expected to what was observed, as well as, the prescriber's subjective |
| measurement of patient's progression to a therapeutic outcome as a percentage of desired response achieved. |

# Support Information

## Registration:

The Intelligent Dosing System's™ product support services are for **registered users only**; make sure that your software is registered with The RxFiles Corporation℠.

## Questions:

If you have questions about the application of the IDS™, please refer to the text of the Help Files first. Then, if you do not find the answer to your question, contact The RxFiles Product Support department by facsimile, e-mail, or telephone at one of the numbers listed below. Before you contact us, it would be best if you were prepared to provide some or all of the following information.

1. Your name, registration number, and the version of the IDS™ that you are using, as well as which agents you are licensed for.
2. The type of hardware and the system configuration that you are using.
3. A description of what happened and what you were trying to do the problem occurred.
4. The exact wording of any messages that appeared on your screen.
5. How you tried to solve the problem.

## Contact Us:

E-Mail us at info@rxfiles.net, or,
Telephone us at (941) 483-3784, or
Fax us at (941) 485-5121.

# Glossary of Terms

## inverse marker

An inverse marker is that marker which moves in opposition or inversely to the dose adjustment. If the dose goes up the marker goes down. If the dose goes down, the marker goes up.

## DoseRx™

Patent Pending 7/14/00) Software products to provide proscribing recommendations. This is part of the IDS™ product offering.

## DRx™

Abbreviation for DoseRx(TM) (Patent Pending 7/1/00.

## IDS™

Abbreviation for the Intelligent Dosing System™ (Patent Pending 7/1/00).

## INR

International Normalized Ratios

## Intelligent Dosing System™

RxFiles.Net-owned tool. 1. (Patent Pending 7/14/00) "Software products to calculate the next best dose." ALSO: 2. (Patent Pending 7/14/00. Will include 15 patent claims.) "Method and system for use in treating a patient with any drug to optimize therapy and prevent an adverse drug response."

## InterchangeRx™

(Patent Pending 7/14/00) "Software products used to change a prescription drug from one brand to another or to a generic."

## IRx™

Abbreviation for InterchangeRx (TM) (Patent Pending 7/1/00).

## Non-Parametric Calculator

Part of the DoseRx software for subjective surrogate markers, or clinical impressions.

## Parametric Calculator

Part of the DoseRx software for objective surrogate markers

## PPRx™

Abbreviation for Practice PrescribeRx (TM) (Patent Pending 7/1/00).

## PRACTICE PRESCRIBERx™

(Patent Pending 7/14/00) "Software products to provide prescribing simulations." This is part of the IDS product offering.

## Surrogate Marker

Any affect a drug would cause on a patient OR any measurable response used to illustrate progress towards an outcome or endpoint. For our purposes, specifically affected by agent, post-agent. Can't be isolated: must be serial, looked at again and again.

# Index

# EXHIBIT 2.2
# THE RxFILES CORPORATION WEBSITE

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# Intelligent Dosing System™ (IDS)™

**The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx a "next" dose calculator, InterchangeRx™, a therapeutic interchanger to switch a patient fi one agent, brand or class of drug to another, and Practice PrescribeRx™, a graded prescr training simulator for new or infrequently used drugs. The IDS™ contains a decision matri and an inference engine encompassed in a designer equation. The equation holds true for drugs.**

All IDS™ products and software can be accessed with Palm Pilot®, Windows®, or Window CE® Operating Systems. Additionally, use of our programs may be submitted for third par reimbursement. The proper CPT codes for all aspects of use are listed in our Reimburser section.

**DoseRx™**

The comprehensive database necessary for the expert environment in our DoseRx™ includes all available information about the subject drug as well as what steady and dynamic state dose is to surrogate marker (concentration) values, and patient findings. A designer equation is then applied with numerical values based on the following parameters: the amount of the subject's last dose, the surrogate marker (SM) response, the current dose, and the desired SM response. The SM can be determined and changed as necessary by the healthcare provider, and can be objective or subjective, positive or negative, based upon the unique combination of circumstances presented by the patient's condition, disease progression, co-morbidities, compliance and therapeutic response.

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**InterchangeRx™**

The InterchangeRx™ software eliminates the concern and emphasis placed on brands or agents being bioequivalent with respect to prescribability and switchability. As bioequivalence is no guarantee of equal therapeutic effect, the InterchangeRx™ method utilizes our Enhanced Intelligence℠ technology to leapfrog to the desired therapeutic effect of the new agent, and calculates whatever dose of the drug is necessary to maintain the established therapeutic effect of the previously used brand or agent. This unique and novel software may also be used if a prescriber desires to change a patient from an agent

belonging in one drug class to another agent in a second class while maintaining a level of pharmacologic therapeutic efficacy. This may require monitoring more than one surrogate marker, that may be of either efficacy or toxicity, or both, as long as they are specifically and serially impacted by either one or both of the agents involved in the switch. The ability to utilize additional markers when changing from one pharmacologic class to another in order to maintain or improve upon an established level of therapy is a unique and valuable characteristic of InterchangeRx™.

**Practice PrescriberRx™**
This program provides graded prescriber training through a computerized simulation of endless "next dose calculation" scenarios, with scalable patient response and surrogate marker inputs. The Practice PrescriberRx™ allows healthcare providers to gain guided and measured experience in calculating the next dose for a new or infrequently used drug. Each simulated experience is graded as compared to the computer, with a cumulative score maintained, so the "student" can self-monitor progress until able to demonstrate a specific or required level of expertise. Unique parameters such as specific disease state, desired treatment outcome, individualized response and compliance level, are all documented for the user. Through this simulation the healthcare provider is educated to the drugs parameters and the appropriate surrogate markers, in relation to both patient and disease, rendering this a thoroughly comprehensive educational experience.

**Practical Applications**

1. **Randomized Concentration Controlled Clinical Trials (RC3T's)™**
   The application of the IDS™ software to the process of drug development vastly increases the speed and efficiency in all phases of clinical trials. Placebo control tri become unnecessary and all volunteers for these trials receive treatment. Applying IDS™ method provides a simple, effective, and economical means to establish anc maintain the optimal therapeutic dose and resultant desired effect. After the IDS™ stabilized all enrollees into the initial "low" stage group, all subjects are evenly divic and randomly assigned to low, medium, and high dose groups. Each level is then monitored, and subjects are moved as necessary into their respective, or optimal, levels of concentration. If a subject "fails" a level, s/he is rapidly moved (titrated) to next level, up or down, and re-evaluated. The end result is a more humane, effecti and informative trial, establishing not only efficacy, but also the optimal dose for specific subject and disease characteristics. There is no reason why this method sh not be the new "Gold-Standard."

2. **Xeno Drug Development**
   As with the RC3T's™, using the IDS™ drug dosing methodology provides a unique opportunity to initiate drug development in other species. The dose response relationship can be illustrated by our three-dimensional mapping technique to facilit the initial understanding of the drugs effect. Through this illustration, both the poten and severity of adverse events can be better controlled and/or avoided. Here again IDS™ provides the means to establish the most safe and effective dose through ra titration in RC3T'™ type testing. Because the IDS™ is accurate with all species use this level is not only possible, but logical and humane as well.

3. **Xeno Transplantation**

In earlier development, a precursor of the IDS™ was used to manage immunosuppressants in the human recipient of a Baboon liver. Even the earlier sys provided the patient with an optimal therapeutic effect without any associated adve events throughout the remainder of his life. While xeno transplantation remains a controversial procedure, and presents an ethical and moral dilemma to which there not currently a generally accepted solution, it is important to know what options ma effectively managed. This knowledge may in fact, eventually assist in the decision process.

4. **Mapping the Surface Response Curve for Additional Drugs**
Requirements for Mapping the Dose Response Curve of any class drug or agent sh include at least 36 observations that track the four specific parameters last dose, la response, current dose, and current response. It is better to have steady-state mark but this is not an absolute requirement. Observations should extend from the low to high end of the normal dosing range of the drug, and there should be at least 12 subjects observed in the low, and 12 in the high range. For most drugs the time between Current Dose and Next Dose should not exceed 30 days. Optimally, the change between Current Dose and Next Dose would be at least 10 percent.

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# The Intelligent Dosing System™ FAQ

**Q. How does the IDS™ work?**

A. The IDS™ works by illustrating the dose-response curve of an agent based upon three-dimensional surface mapping. The 3-D mapping results in a linearity factor that is integrated into a designer equation attached to a stochastic patient control loop to meter the dose in response to a surrogate marker which may be objective, subjective, positive or negative.

**Q. What do you mean by surrogate markers?**

A. A surrogate marker is any observation or measurement that can be taken from a patient that relates to the level of drug in the body, which in turn relates to the efficacy or toxicity of the drug. Surrogate markers could also be a physician's clinical impression, or, the result of several observations and/or measurements. This point demonstrates how the IDS™ works for and with the physician, as a tool, to improve patient dosing and care.

**Q. Can one use various surrogate markers to dose a patient?**

A. Yes. The 3-D mapping results in a linearity factor that is integrated into a designer equation attached to a stochastic patient control loop to meter the dose in response to a surrogate marker which may be objective, subjective, positive or negative. This means that our discovery allows any patient to be dosed on an agent based on either a positive marker such as plasma concentration, blood pressure or viral load, or a negative marker of toxicity such as a change in absolute neutrophil count, anemia, serum creatinine or the number of episodes of diarrhea. In fact, the open loop allows for several markers to be used simultaneously, with the understanding that each one is calculated separately.

**Q. How does the IDS™ individualize patient therapy?**

A. The IDS™ is based on the patient's previous dosing experience. It is designed to address the individual's response, and aid the physician in maintaining the optimal therapeutic effect. The plane of fit is further optimized for the individual patient by utilizing the open loop to reconfigure the plane to a three-dimensional curve.

**Q. What does the IDS™ Matrix use to dose?**

A. Archetypes of the IDS™ had the ability to use only drug blood levels, but our newest discovery, resulting in a new patent application, allows the IDS™ Matrix to dose to any surrogate marker; those that are objective or subjective, including the physician's clinical impression, and those that are indicative of therapeutic efficacy or toxicity.

**Q. Will the IDS™ Matrix replace the physician?**

A. No. The IDS™ was designed as a tool for the physician to guide drug therapy. The IDS™ simply provides a standardized "map" for the individual's expected dose to level relationship.

**Q. How is it that the IDS™ technology can predict the dose-level relationship when modern PK-PD technology cannot?**

A. Classical PK-PD methodology was designed as a descriptive science, and so it remains today. While appreciating the traditional applications of PK and PD, our technology provides the "roadmap," and therefore the opportunity to combine technology and make a more significant improvement in patient care. The IDS™ Matrix is predictive rather than descriptive. With this in mind, the IDS™ is better suited for patient dosing.

**Q. Should the IDS™ Matrix be used for all drugs?**

A. The best utilization of the Matrix in drug therapy comes from use with drugs that are inherently difficult to manage. Drugs with a narrow therapeutic index or range, and drugs with numerous or severe toxicities are the best candidates.

**Q. Are there populations of people that are better suited for the IDS™ Matrix?**

A. The IDS™ Matrix works and individualizes drug therapy for any population. However, children, because of their higher metabolic state, require more drug for a response. Therefore, it is the pediatric population that receives the most benefit from the Matrix, due to their being on the most non-linear portion of the plane of fit for a drug.

**Q. What kind of drugs, and how many different ones can the IDS™ methodology be applied to?**

A. In February 2000 at the CASE CDER seminar we were tasked by the FDA to apply the technology to certain therapeutic categories. Those areas included Warfarin Na, Phenytoin, Digoxin, Insulin Gentamicin, Tobramycin, Vancomycin, thyroid products, Chemotherapeutics, HIV Agents, Heparin, Oral Hypoglycemics, Antihypertensives and the Statins. Agents we are currently working on include the Anti-depressants Prozac and Remeron, the Anti-psychotics Risperidal and Zyprexa, chemotherapeutics such as Xeloda, Taxol, Gemzar, Platinol, analgesics such as Morphine and the NSAIDS, combination Bronchodilators, Accutane, Oxygen and Potassium.

**Q. What is the difference between parametric and non-parametric dosing with the IDS™?**

A. Our parametric dosing system allows the input of either positive or negative objective markers. Additionally, our designer equation allows us to dose a patient non-parametrically such that a sliding scale allows the prescriber to enter the prescriber's subjective evaluation with regard to how the prescriber would gauge the patient's last change in response, as a percentage of what was expected to what was

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observed, as well as the prescribers subjective measurement of the patient's progression to a therapeutic outcome as a percentage of desired response achieved.

# EXHIBIT 2.3
# PRODUCT LITERATURE

WE'VE DISCOVERED THE DOSE RESPONSE CURVE FOR EVERY DRUG.
EVERY DISEASE AND EVERY PATIENT.

REVO[illegible] AND DISEASE.

**The Intelligent Dosing System™ (IDS™):**

THREE-PART SOFTWARE SUITE FOR PC, PALM AND WIN CE USERS FEATURES...

**DoseRx™**

**InterchangeRx™**

**Practice PrescribeRx™**

**IDS™ DRUG DEVELOPMENT APPLICATIONS:**

- ILLUSTRATES THE DOSE RESPONSE CURVE OF ANY AGENT
- ACCELERATES THE DRUG DEVELOPMENT PROCESS
- ELIMINATES PLACEBO CONTROL TRIALS
- EASILY MANAGES RANDOMIZED CONCENTRATION CONTROLLED CLINICAL TRIALS℠
- PRODUCES UNIFORM RESULTS FROM MULTI-CENTER TRIALS

**IDS™ POST APPROVAL APPLICATIONS:**

- ABBREVIATE THE NEW DRUG ACCEPTANCE/USE SEQUENCE
- DOSE TO ANY SURROGATE MARKERS, OBJECTIVE OR SUBJECTIVE, POSITIVE OR NEGATIVE
- GREATEST EXPERTISE AVAILABLE FOR EACH DOSE CALCULATION
- GRADED PRESCRIBER CASE SIMULATIONS
- THERAPEUTIC INTERCHANGER

Pat[illegible]

The RxFiles.Net Corporation is a healthcare technology development company with original hardware and software products for clinical practice and medical research. Our innovative products promote safer, more effective and less costly individualized patient care.

For more information contact us at 1.877.RxFiles, or e-mail Info@RxFiles.Net or visit our website www.RxFiles.Net

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The RxFiles.Net [illegible]

# SECTION 3
# EQUATION FORMULA

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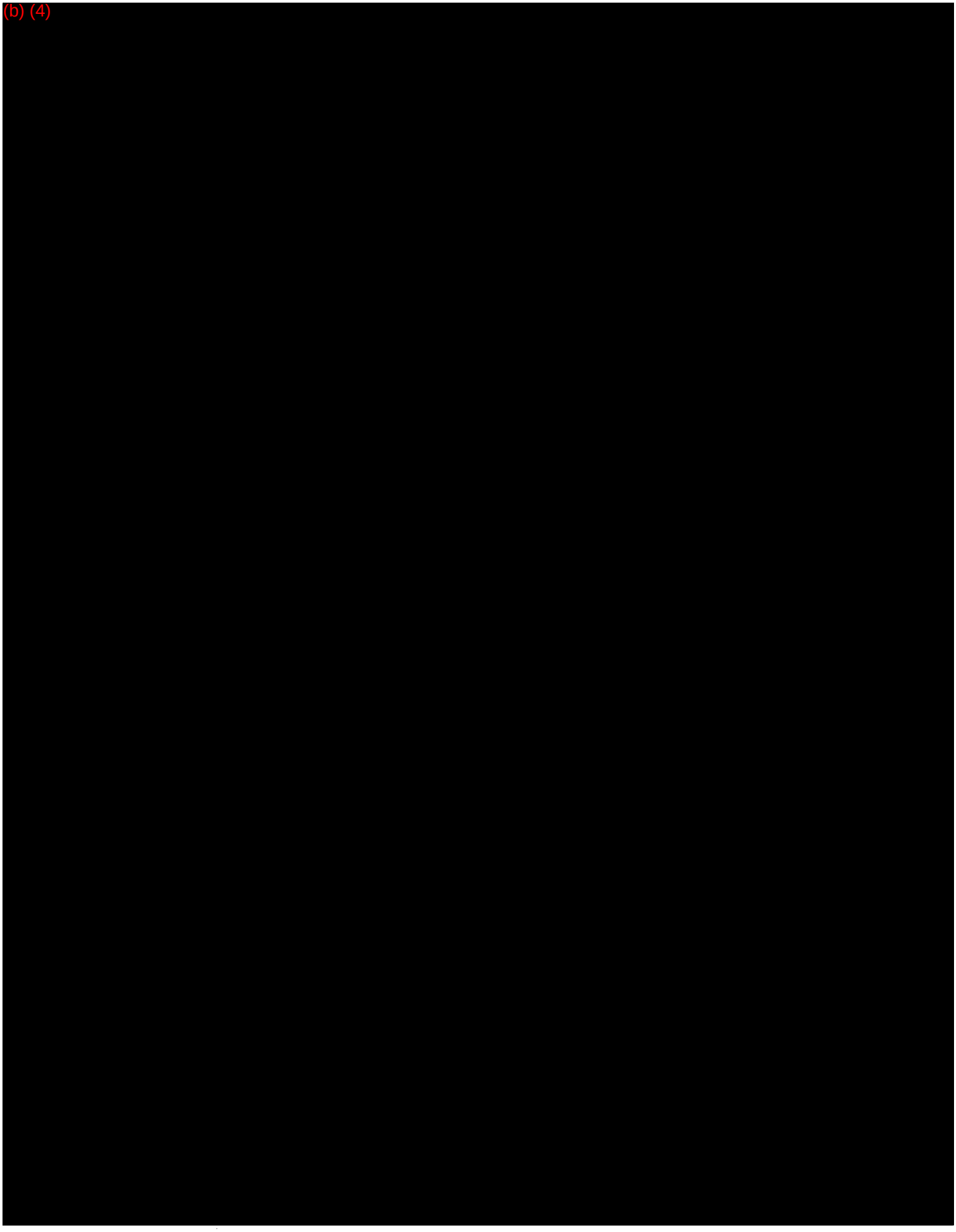

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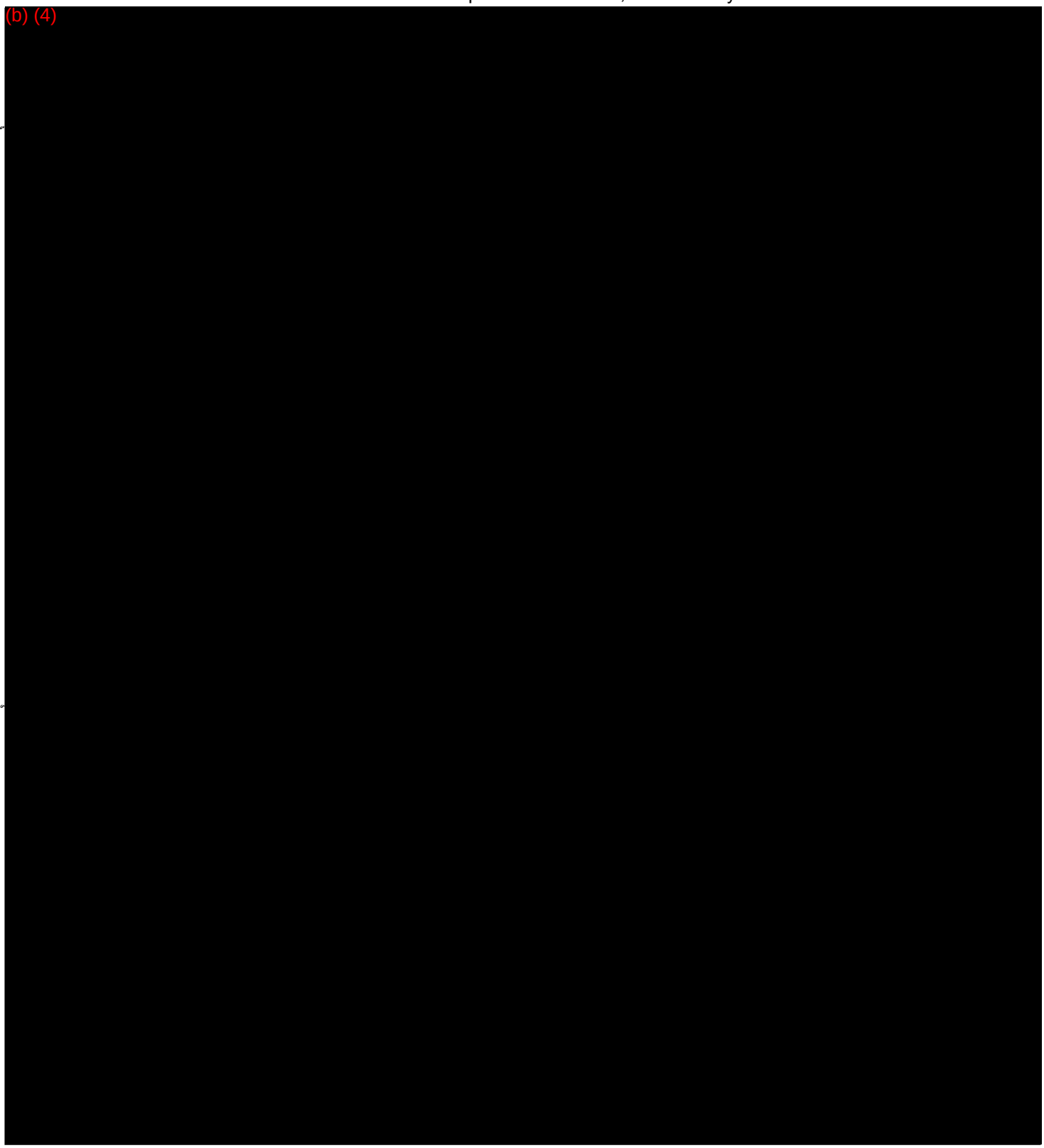

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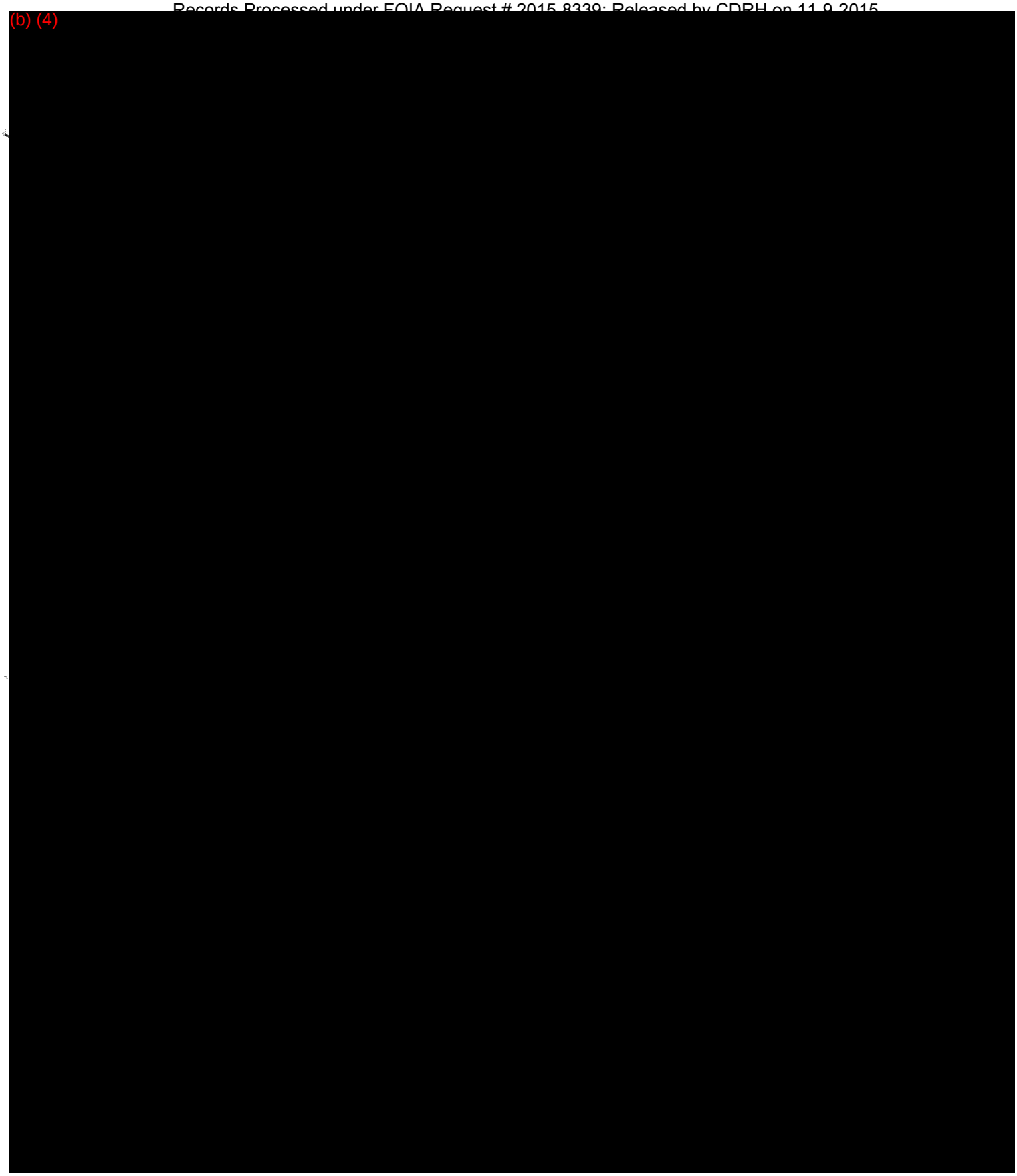

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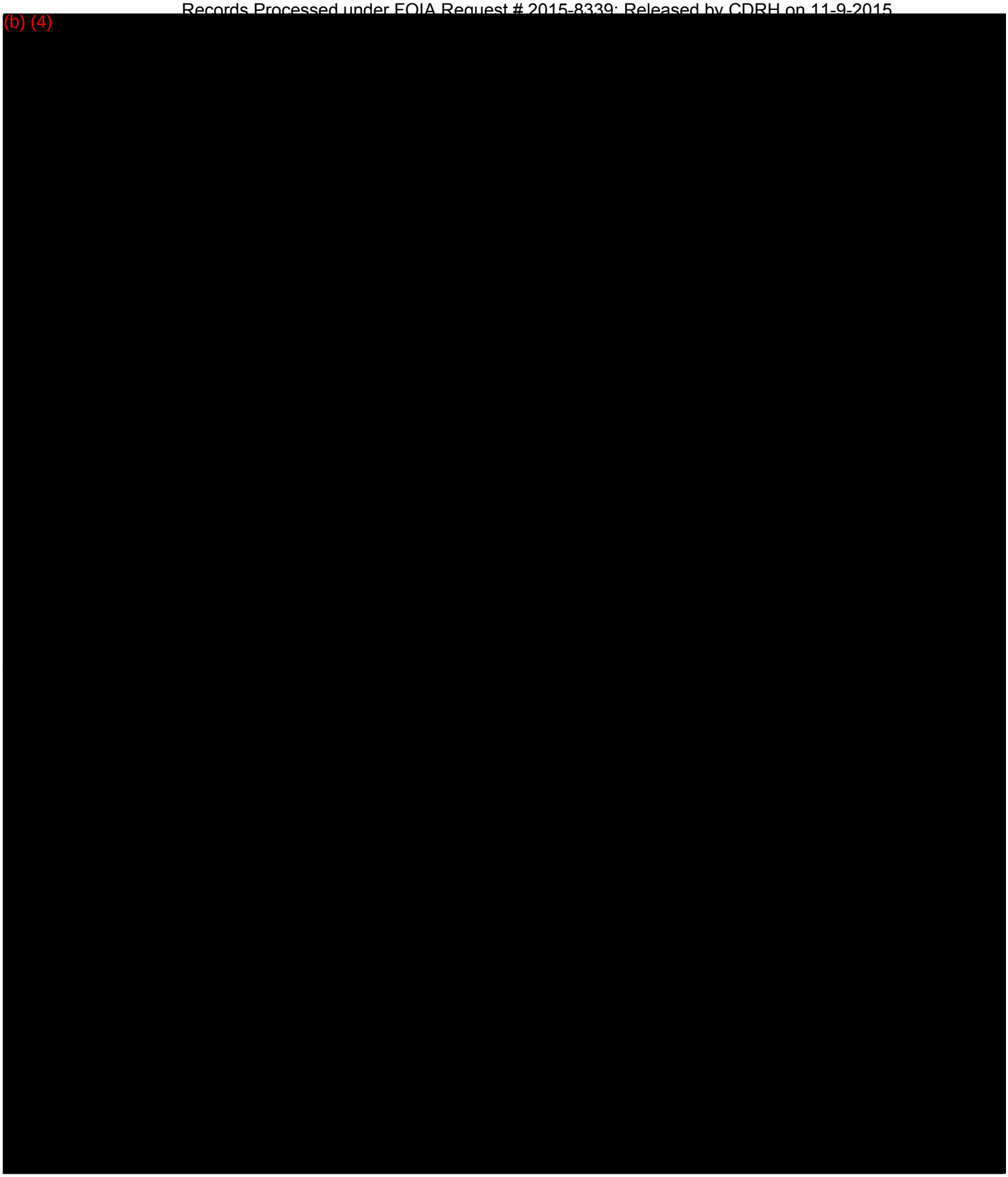

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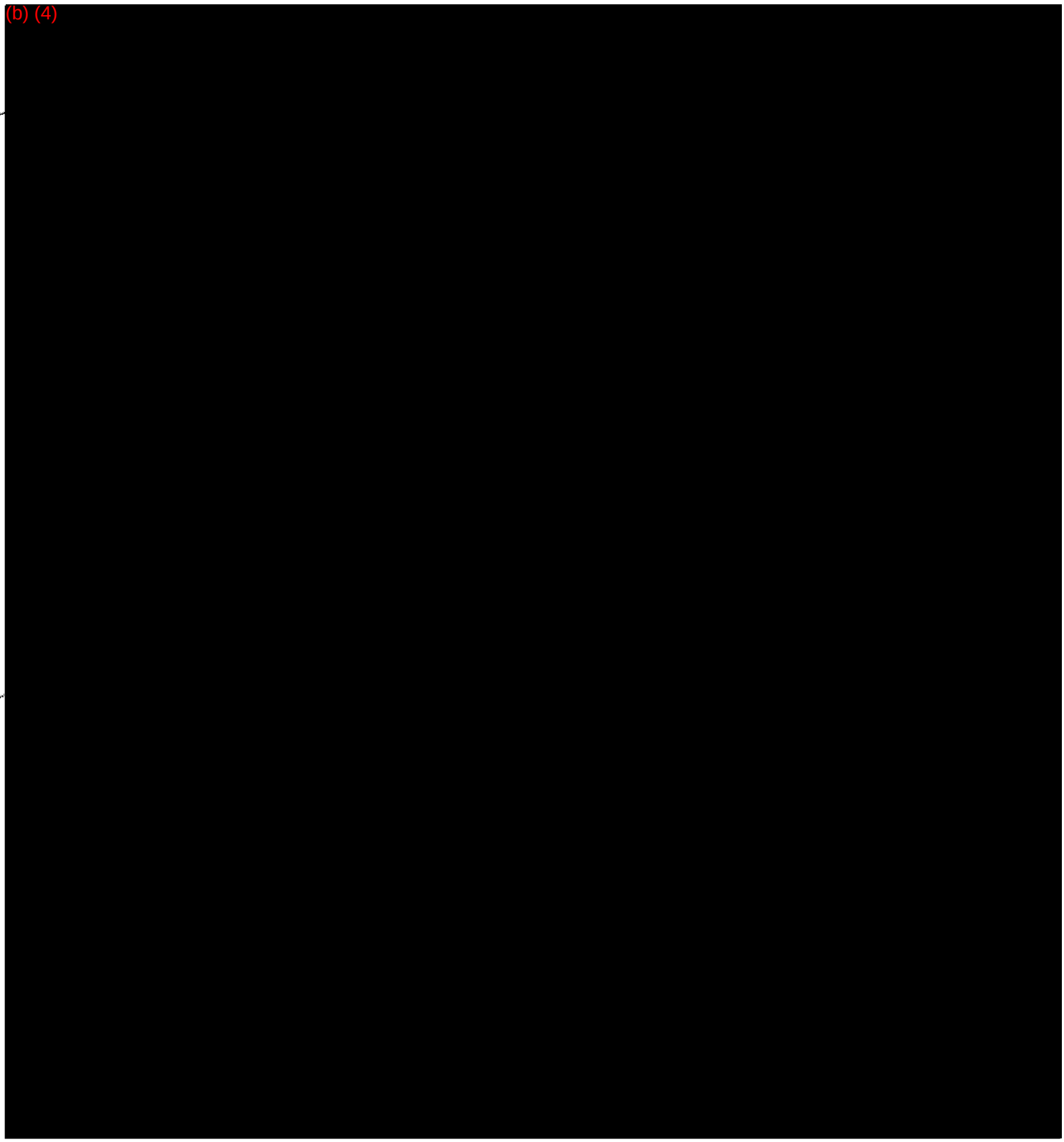

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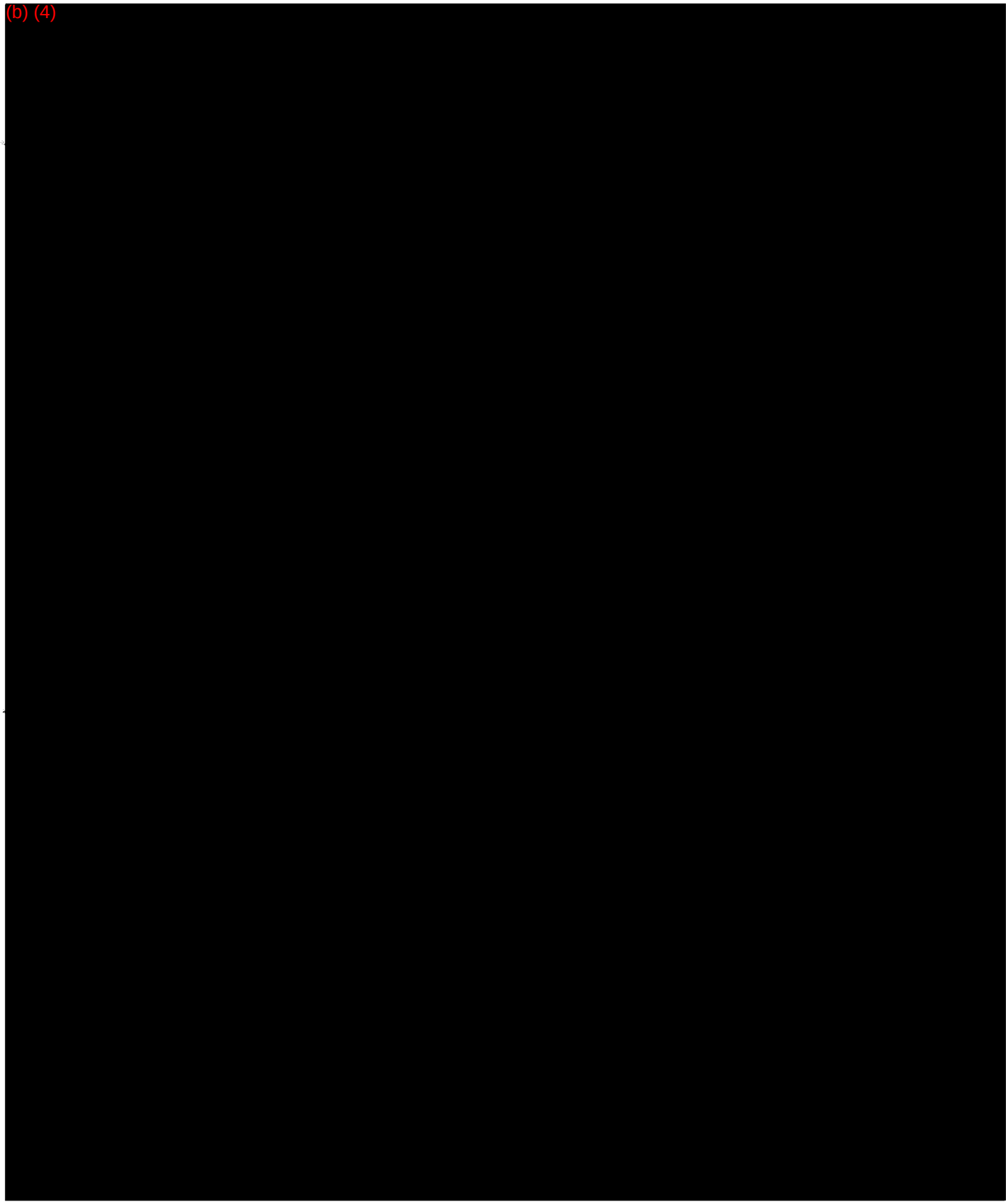

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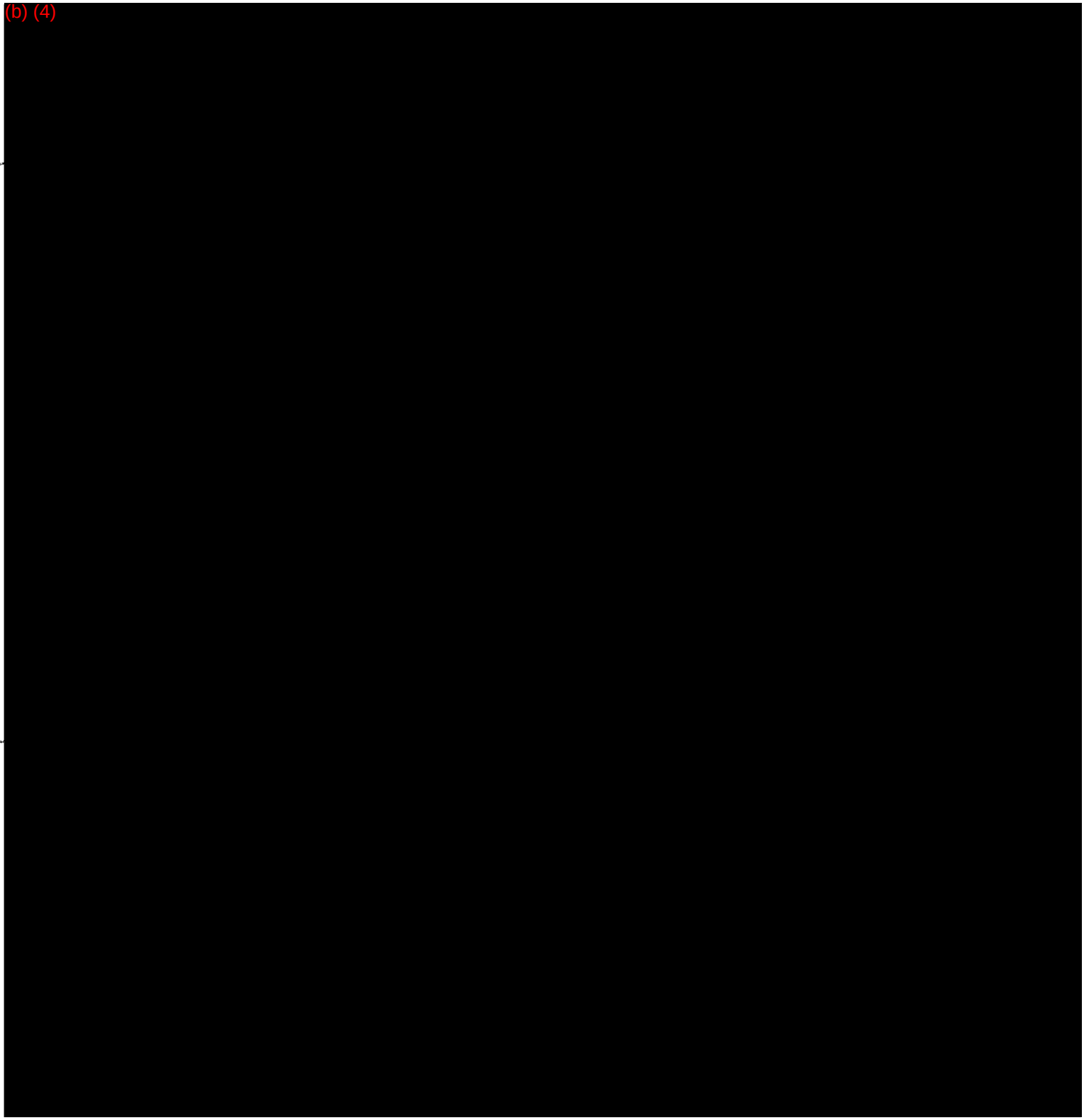

# SECTION 4
# HAZARD ANALYSIS

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# SECTION 5
# SOFTWARE REQUIREMENTS SPECIFICATIONS







b2

# SECTION 5: SOFTWARE REQUIREMENTS SPECIFICATIONS

**Hardware Platform:**

(b) (4) [redacted]

**Program Language:**

(b) (4) [redacted]

**Program Size:**
276 kb

**Interface requirements:**
Monitor, keyboard, mouse, printer if desired for records. Or – PDA and stylus

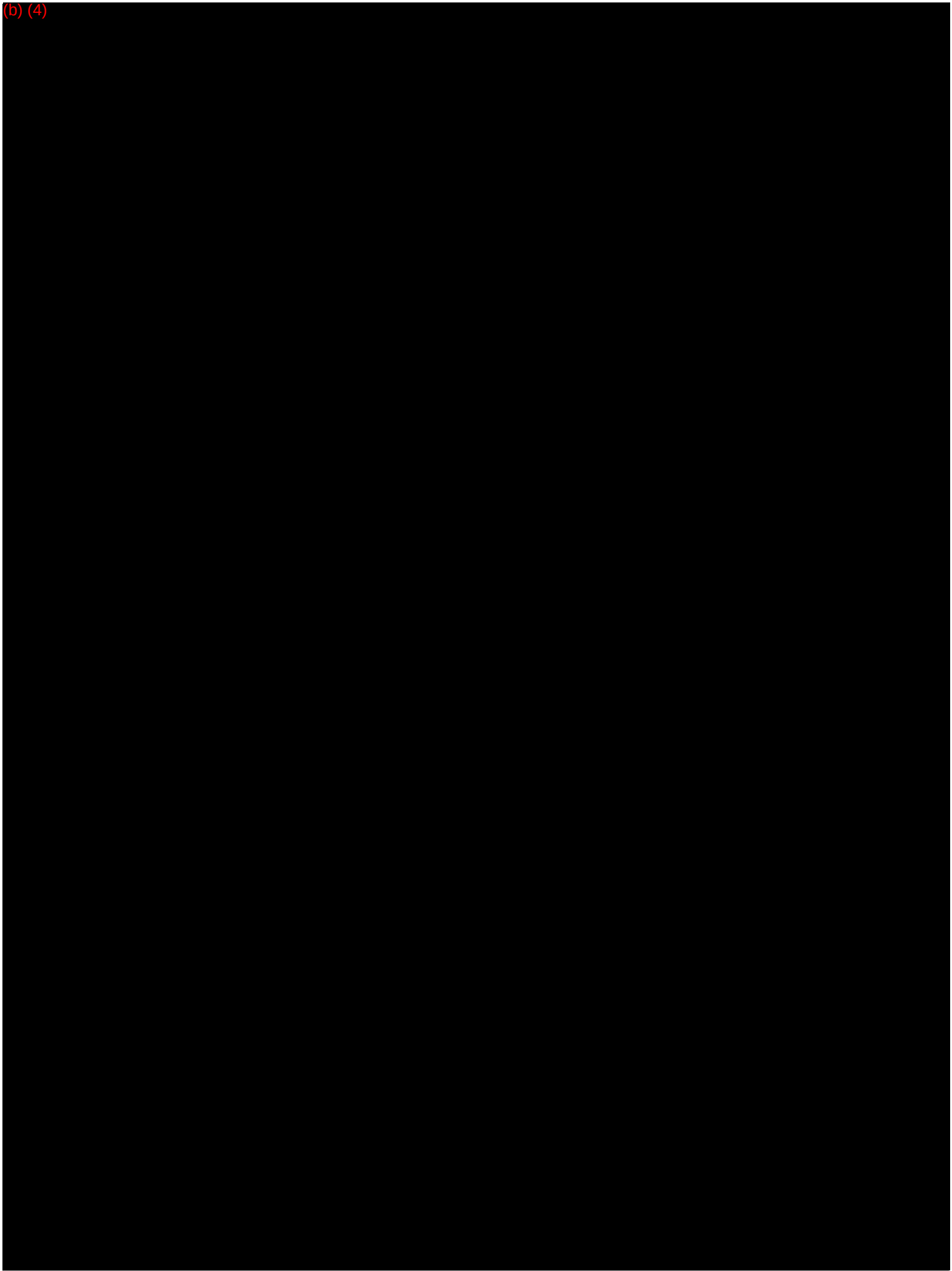
Software performs as a calculator for three dimensional response curve. It requires input of last dose and response. It does not need an alarm, it has no limitations due to the software. It has one screen in the help files for a sample dose scenario, users can test their calculator against that sample. No fault detection is necessary, either the calculator, run by user hardware, is working or there is a hardware failure and it is not. Current version does not have timing or memory requirements. The IDS™ uses no "off the shelf" software.

**Development Requirements:** Reference Exhibit 5.1

**Software Requirements Specifications:** Reference Exhibit 5.2

**Software Performance:**
***Documentation of Improvement: RxFiles Corporation Systems Modification Log*:** Reference Exhibit 5.3

# EXHIBIT 5.1
# DEVELOPMENT REQUIREMENTS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# Activity Requirements - Evaluate Implementation of Agent to be Dosed, Continued

**Generic Formulae for Any Agent Doser – Stochastic Open Loop**

The formulae for the stochastic open loop which mitigates the various factors which can influence a subject's Marker is as follows:

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# EXHIBIT 5.2
# SOFTWARE REQUIREMENTS SPECIFICATIONS

| Location In SRD = Page # Or document named | FDA 50L - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices |
|---|---|
| | **Section3. Documentation in a Premarket Submission** |
| | Submissions for Software Contained in |
| Separate Document | **3.1 Level of Concern** |
| | **Medical Devices** |
| Substantiation of sales claims document | Provide the level of concern of your software, and the supporting rationale (see Section 2 for details). If the level of concern is major, and you have not previously submitted a premarket submission for this type of device to ODE, it is strongly recommended that you contact the appropriate division prior to making the submission |
| | 2.2 Approach Recommended by FDA for Risk Estimation and Control |
| | 2.2.2 Decision Process |
| | 3. Does the device software control treatment delivery, such that an error or malfunction with the delivery could result in death or serious injury? |
| | Identification of Hazards - SRD pages 46-50 |
| | Hazards resolution - SRD pages 52 - 57 |
| | **3.2 Software Description** |
| 14-21 | Provide a comprehensive overview of the device features that are controlled by software, and describe the intended operational environment. |
| | 3.2.1 Device Features Controlled by Software |
| 6-13 | What is the role of the software in your medical devices? What does the software do, and as important, what does the software NOT do? How does the user interact with the software? What software functions can be controlled or modified by the user, and which are unchangeable? Which, if any, of the software features have hardware over-rides or backups? This information should generally be provided in paragraph format, and should highlight major/significant software features. A detailed description of software requirements is addressed under subsection 3.5, Software Requirements |
| | 3.2.2 Operational Environment |
| | The description of the intended operational environment should include the following: |
| 4 | programming language |
| 4 | hardware platform |
| 4 | operating system (if applicable)* |
| None | use of Off-the-Shelf components (if applicable)* |
| None | * If your device uses Off-the Shelf components, please refer to FDA's (draft) Guidance for Off-the-Shelf Software Use in Medical Devices (see Appendix C.6). |
| | **3.3 Device Hazard Analysis** |
| | Submissions for any level of concern should contain a device hazard analysis that takes into account all device hazards associated with its intended use, hardware, and software. The hazard analysis should include the following: |
| 46, 57 | a) the hazardous event; |
| 46, 57 | b) level of concern of the hazard; |
| 46, 57 | c) the cause(s) of the hazard; |
| 46, 57 | d) the method of control; |
| 46, 57 | e) corrective measures taken, including aspects of the device design/requirements, that eliminate, reduce, or warn of a hazardous event, including a discussion of their appropriateness; and |
| 46, 57 | f) testing to demonstrate that the method of control was implemented correctly. |
| 50 | This information is typically presented in a tabular format. When performing a hazard analysis, manufacturers should be careful to include all foreseeable hazards, including those resulting from intentional or inadvertent misuse of the device. |
| 50 | There are times when a fault tree analysis of the software is useful. For each identified hazard, a detailed analysis should be carried out to discover the conditions which might cause that hazard (see (c) above). There are various techniques, one of which is a fault tree analysis which involves identifying the undesired event and working backwards from that event to discover the possible causes of the hazard. |
| | **3.4 Software Requirements Specification (SRS)** |
| 1- 82 | The Software Requirements Specification documents the requirements for the software. This typically includes functional, performance, interface, design, and developmental requirements. Examples of some typical requirements that would be included in a SRS include: |
| 9 | a) hardware requirements, including microprocessors, memory devices, sensors, energy sources, safety features, communications, etc.; |
| 4 | b) programming language and program size(s); |
| | c) interface requirements, including both communication between system components and communication with the user (e.g., printers, monitors, keyboard, mouse, etc.); |
| | d) software performance and functional requirements, examples of which include: |
| 14 - 29 | - algorithms or control characteristics for therapy, diagnosis, monitoring, alarms, analysis, and interpretation (with full text references or supporting clinical data if necessary), |
| 14 - 29 | - device limitations due to software, |
| 14 - 29 | - internal software tests and checks, |

| | |
|---|---|
| 14 - 29 | - error and interrupt handling, |
| 14 - 29 | - fault detection, tolerance, and recovery characteristics, |
| 14 - 29 | - safety requirements, |
| 14 - 29 | - timing and memory requirements, |
| 14 - 29 | - identification of off-the-shelf software (if appropriate). |
| none - major | For a minor concern device, it is usually sufficient to provide only the functional requirements section from the SRS. For moderate and major concern devices, the complete SRS should be provided. |
| | **3.5 Architecture Design Chart** |
| 48 | For minor level devices, submissions should contain a chart depicting the partitioning of the software into its functional subsystems. Note, it is not necessary to include each and every software module. The chart should depict the software architecture at the functional level.<br>For moderate and major concern devices, the chart should be more detailed, although still focused at the functional level. The submission should also include a list of functional modules, and a description of the role that each module plays in fulfilling the software requirements. |
| | **3.6 Design Specification** |
| 1- 82 | The software design specification is a description of what the program should do and how it should do it. It should both provide a high level summary of the design and specifications detailed enough such that a programmer is not required to make ad hoc design decisions. The software design specification should include documentation of the elements listed below, and will likely reference separate documentation for some of these elements: |
| 6,7 | • Software Requirements Specification, including predetermined criteria for acceptance of the program; |
| 9 | • Development standards and programming standards; |
| 40 | • Hazard Analysis; |
| Jan-82 | • Systems documentation (context in which the program is intended to function, e.g. systems documentation narrative or context diagram); |
| 4 | • Hardware to be used; |
| 18, 24 | • Parameters to be measured or recorded; |
| 19-22 | • Logic (logical structure, control logic, logical processing steps); |
| 30,74 | • Data Structures and data flow diagrams; |
| 20-23,28 | • Definitions of variables (control and data) and description of where they are used; |
| None | • Error and alarm messages; |
| See Overviews PMS,VMS, DMS | • Supporting software (e.g. operating systems, drivers and other application software); |
| 59, 71 | • Communications links (links among internal modules of the software, links with the supporting software and links with the hardware); and |
| 70, 76 | • Security measures (both physical and logical security). |
| | **3.7 Traceability Analysis** |
| PMS | Provide a traceability analysis or matrix which links requirements, design specifications, hazards, and validation. Traceability among these activities and documents is essential. This document acts as a map, providing the links necessary for determining where information is located. Although it is possible to document traceability through a shared organizational structure and common numbering scheme, appropriate information should be provided to guide the review through the information included in the submission. |
| | **3.8 Development** |
| None Needed | For moderate and major concern devices, sponsors should provide a summary (typically no more than 2-4 pages) of the software development life cycle plans. The summary should describe the processes that are in place to manage the various software development life cycle activities. Also for moderate concern devices, sponsors should provide a summary of the configuration management and maintenance plans. |
| 12 | In addition, for major concern devices, the submission should include an annotated list of the control/baseline documents generated during the software development process, as well as the configuration management and maintenance plan. |
| | **3.9 Validation, Verification and Testing** |
| 46-51 | Software verification involves a systematic application of various analyses, evaluations, assurances, and testing of the software and its supporting documentation at each stage of the software development process, to assure that all the requirements specified for that stage have been fulfilled. Software validattion uses similar analytical techniques, but goes further to assure, to the extent possible, that the finished device (with its incorporated software) is appropriate for its intended use and will be reliable, and safe. |
| | The following test information should be provided: |
| none | a) for a device in which the software is considered of minor level of concern:<br>- a software functional test plan with pass/fail criteria, data, and an analysis of the results; |
| none | b) for a device in which the software is considered of moderate level of concern:<br>- a description of the verification activities at the unit, integration and system level,<br>- a system level test protocol including pass/fail criteria, and test results; |
| 46-51 | c) for a device in which the software is considered of major level of concern: |
| 50 | - a description of the verification activities at the unit, integration and system level, |
| 51 | - unit, integration and system level test protocols including pass/fail criteria, test report, summary, and test results. |

| | | |
|---|---|---|
| check lists provided by JDK and MG | | All testing information should include the version and revision identifiers for the software and a discussion of testing results should include a discussion of how the following was tested (when applicable): |
| 49 | | - fault, alarm, and hazard testing, |
| 49 | | - error, range checking, and boundary value testing, |
| 49 | | - timing analysis and testing, |
| 49 | | - special algorithms and interpretation tests and analysis, |
| 49 | | - stress testing, |
| 49 | | - device options, accessories, and configurations testing, |
| 49 | | - communications testing, |
| 49 | | - memory utilization testing, |
| none | | - qualification of off-the-shelf software (see Appendix C.6), |
| 49 | | - acceptance and beta site testing, and |
| 49 | | - regression testing. |
| | **3.10 Revision Level History** | |
| 55, 56,58 | | For moderate and major concern software, the submission should include the revision history log, documenting all major changes to the software during its development cycle. |
| | **3.11 Unresolved Anomalies (Bugs)** | |
| 58-61 | | For moderate and major concern software, the submission should include a list of all unresolved software anomalies. For each anomaly, indicate the problem, the impact on device performance, and, if appropriate, any plans or timeframes for correcting the problem. This list of bugs should be communicated to the user in the device labeling. |
| | **3.12 Release Version Number** | |
| 18, 30, 46, 59, 65, 74 | | For all levels of concern, the submission should include the release version number and date for the software that will be included in the marketed device. |
| | **4.1 Life Cycle Models and Development Methodologies** | |
| 40, 44 | | The software life cycle is a microcosm of the entire device life cycle. The manufacturer can choose a software life cycle model and development methodology that is appropriate for their device and their organization. Generally, the life cycle model selected should include activities for risk management, requirements analysis and specification, design (both top level and detailed), implementation (coding), integration, validation, and maintenance. A software life cycle model should be understandable, thoroughly documented, results oriented, auditable, and traceable, and should promote appropriate feedback within the development process. "Code-and-fix" is a commonly used, but not very effective approach to the software life cycle, because it provides no means for identifying risks, assessing quality, and identifying and eliminating anomalies early in the development process. |
| Iterative | | There are a variety of life cycle models, such as: waterfall, spiral, evolutionary, incremental, top-down functional decomposition (or stepwise refinement), formal transformation, etc. Medical device software may be produced using any of these or other models, as long as adequate risk management activities and feedback processes are incorporated into the model selected. It is feasible to intermix different life cycle models and methodologies among subsystems and subcomponents (i.e., hardware, software, materials, etc.). Terminology from model to model and methodology to methodology may vary. A generic life cycle model is depicted in Figure 3, depicting the relationship of risk management activities to life cycle activities. |
| | **4.2 Requirements Analysis and Specification** | |
| 6 | | Early in the device design process, there is an activity which identifies and analyzes customer or end-user functional and performance requirements for the device, and determines which of those device (system) requirements will be allocated to software. It is important to define the role of the software in the device at this time, in particular with regard to risk-related functions. During this requirements activity, the functions to be performed, controlled, or monitored by the software are documented. Software quality characteristics, such as human factors, functional characteristics, response times, output, safety requirements, etc., are defined, along with acceptance criteria. |
| 46 | | Software safety requirements are derived from the preliminary hazard analysis and ongoing risk management activities, as requirements are updated throughout the life cycle process. Any hazardous software functions are identified, evaluated, and traced to be able to show subsequent mitigation of the risk associated with those functions to an acceptable level. |
| | **4.3 Risk Management** | |
| 46 | | Risk management is a combination of risk analysis and risk control activities. Risk analysis is used to estimate the risk associated with the use of the device, and risk control is used to mitigate the risk to an acceptable level. It is normal for a manufacturer to have a risk management plan that is used to define and control the risk analysis and risk control activities. These activities are ongoing throughout the device life cycle. Risk analyses should be performed for the device as an entity, as well as major components/subsystems. Appropriate techniques should be chosen so that risk analyses for the software, electronics, biomaterials and so forth, can be effectively integrated and analyzed at both the device level and at the subsystem level. |
| | | Several national and international consensus standards, such as those cited in Appendix B, can assist manufacturers during this process. |
| | | There are many dimensions to risk, for example: cost, integrity, security, safety, etc. For FDA's review of medical devices, the primary focus is on the safety dimension of risk. Software risk management is a subset of the overall risk management of the device. Risk is reduced when the severity of the consequence of the hazard is reduced and/or the likelihood of the hazard occurrence is reduced. When a hazard is specifically linked to the software, the likelihood of hazard occurrence is directly related to the failure rate of the software. The calculation of accurate software failure rates is difficult, if not impossible. Therefore, risk reduction and mitigation techniques for software should be employed to control the severity of a hazard assuming that the likelihood of occurrence is unacceptably high. |

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|---|---|
| | **4.3.1 Risk Analysis Activities** |
| 46 | Risk analysis includes hazard analysis and risk estimation. Hazard analysis provides documented identification for potential device hazards. Potential device hazards are identified for all reasonably foreseeable circumstances. Hazard analysis is conducted in accordance with established procedures. It should begin early in the life cycle, as requirements are established, and should be updated as development progresses, to assess the effectiveness of hazard mitigation and whether any new hazards have been introduced. Device hazards should be considered for their effect on the following: patients, operators, bystanders, service personnel, and the environment. |
| 46 | For each identified hazard, a list of possible initiating causes is developed. Initiating causes can come from any of the following areas: human factors, hardware faults, software faults, integration errors, and environmental conditions. A variety of methods can be used to perform the hazard analysis (e.g. fault tree analysis, failure modes and effects analysis). In general, different methods will be used during different phases of the development life cycle as more becomes known about the end product. The manufacturer is expected to select the appropriate methods for their device and its intended use. For purposes of this document, a software related hazard is defined as any device hazard that has its initiating cause or a major contributing cause in software. For software related hazards, the hazard analysis documentation should identify traceability from the device level down to the specific cause in the software. |
| 46 | Risk estimation is conducted for each identified hazard. The risk estimation is based on the severity of resulting consequences and the likelihood of occurrence. For each hazard a severity level should be assigned. Severity levels can be defined using the level of concern terminology (major, moderate, and minor) used in this document. |
| 46 | For each hazard, a likelihood of occurrence should be assigned. In the case of software related hazards, one component of this likelihood is directly related to the software failure rate. The software failure rate is the result of systematic (versus random) software faults. Due to the nature of systematic faults, the accurate estimation of software failure rates is difficult. Unless the accuracy of the software failure rate can be confirmed it will not be appropriate to control risk based on estimated software failure rate. For software related hazards, software failure rates need not be calculated if the manufacturer assumes that the software failure rate is at an unacceptable level. Using this approach, the manufacturer will be able to concentrate resources on creating design solutions that reduce and/or eliminate the severity of hazards. |
| 46 | A device may have multiple potential hazards associated with it. Likewise, each hazard may have multiple potential causes. The goal should be to identify all potential causes for each hazard. The degree of effort and detail in characterizing potential causes of a hazard should be commensurate with the severity of resulting consequences. The methods used to identify hazards and their causes, and to categorize severity should be documented. |
| | **4.3.2 Risk Control Activities** |
| | Risk control is intended to eliminate a hazard or to mitigate the estimated risk to an acceptable level. Risk control methods are directed at the cause of the hazard. Several risk control methods and their priority are as follows: |
| 47,48,49,50,51 | 1. eliminate or reduce the risk by inherent safe design or redesign; |
| 52 | 2. reduce the risk by protective measures; and |
| 52-57 | 3. reduce the risk by adequate user information, such as sufficient warnings. |
| 57 | For each identified hazard, the manufacturer should identify the risk control method that was used to eliminate the risk or reduce the risk to an acceptable level. For each software related hazard, the manufacturer should indicate the severity level after the risk control method has been implemented. The goal is to reduce all software related hazards to a minor level of concern. |
| | A determination is made about the appropriateness of the residual risk for each hazard/cause combination. Following this, a determination is made as to whether or not the risk control measures introduced any new hazards. If so, the process is repeated. Referring to Figure 4, steps 2 through 7 are repeated for each potential hazard while steps 4 through 6 are repeated for each potential cause. After all potential hazards have been evaluated, a final determination is made about the device safety. |
| | **4.3.3 Documentation** |
| | Several work products result from the ongoing risk management process. A hazard analysis by itself is not sufficient. Manufacturers should also document: |
| 46 | 1. a description of the identified hazard; |
| Substantiation of sales claims document operational ranges | 2. the severity level of the hazard (major, moderate, or minor); |
| 46 | 3. the specific software cause of this hazard, so it can be traced to the specific location in the software; |
| 49, 50, 51 | 4. risk control method employed; |
| | 5. test or verification method used to confirm the risk method employed; and |
| 49 | 6. severity level of the hazard after the risk control method has been implemented. |
| 50 | - what the estimated severity of each hazard is and how it was categorized; |
| 51 | - what risk reduction and mitigation techniques were implemented and how their effectiveness was assessed; and |
| | - testing and evaluation demonstrating the implementation of the safety features. |

Pages 207 through 288 removed.

# EXHIBIT 5.3
# Documentation of Improvement: RxFiles Corporation Systems Modification Log

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# The RxFiles Corporation
# Project Management System

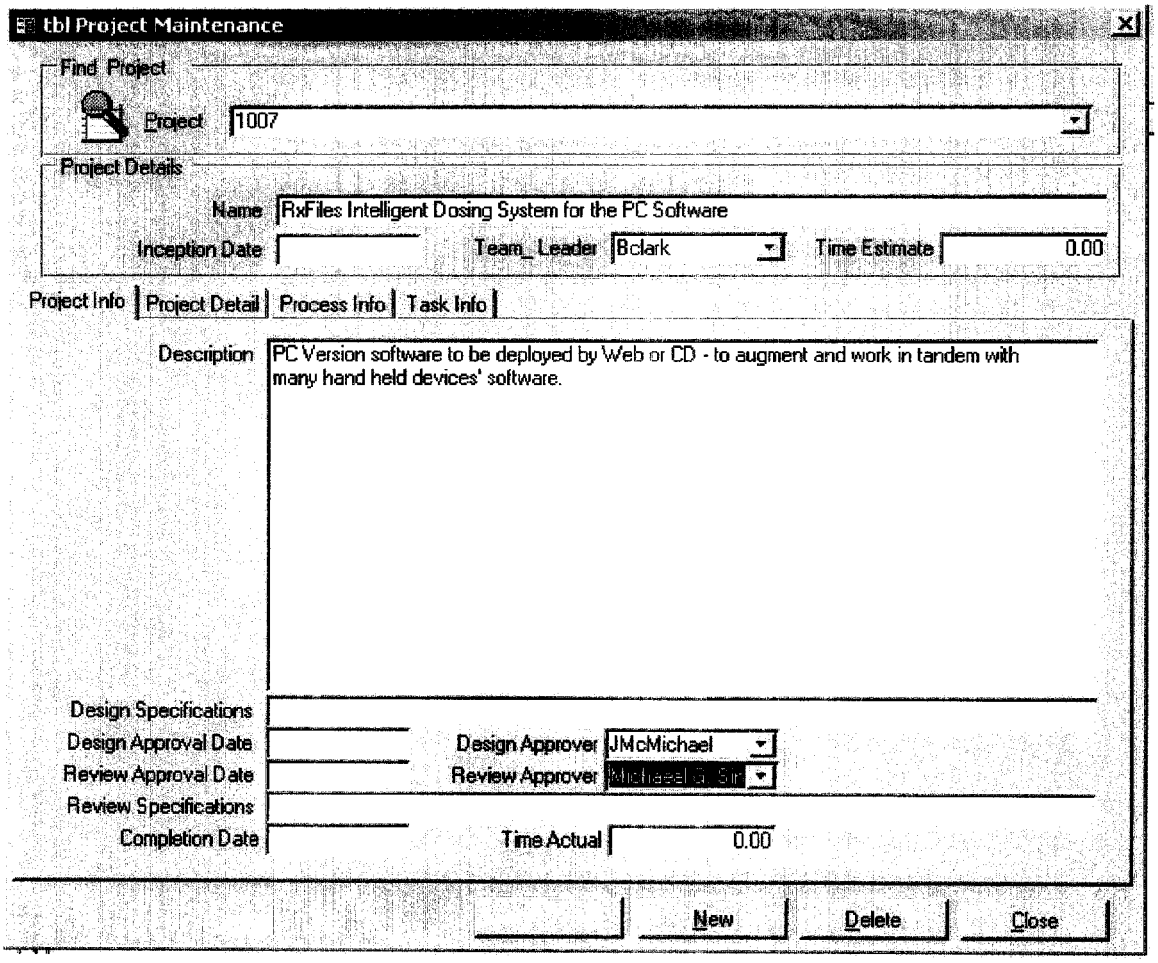
## Focus Statement

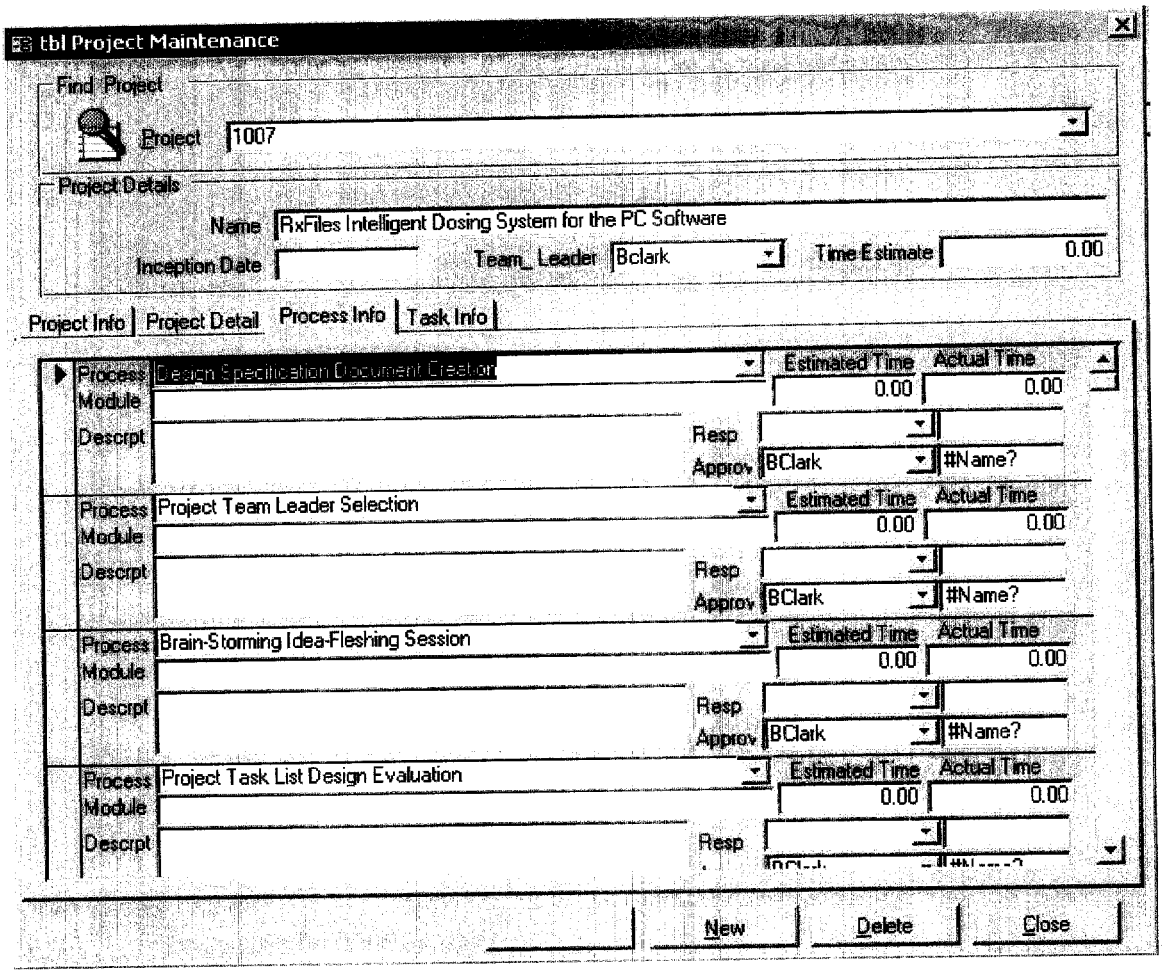
TheRxFiles Corporation's **Project Management System (PMS)** was instituted to **register, document and track** the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation **stage completion history** of each enterprise project conceived, ratified and generated by the Firm for Firm wide use.

# Overview

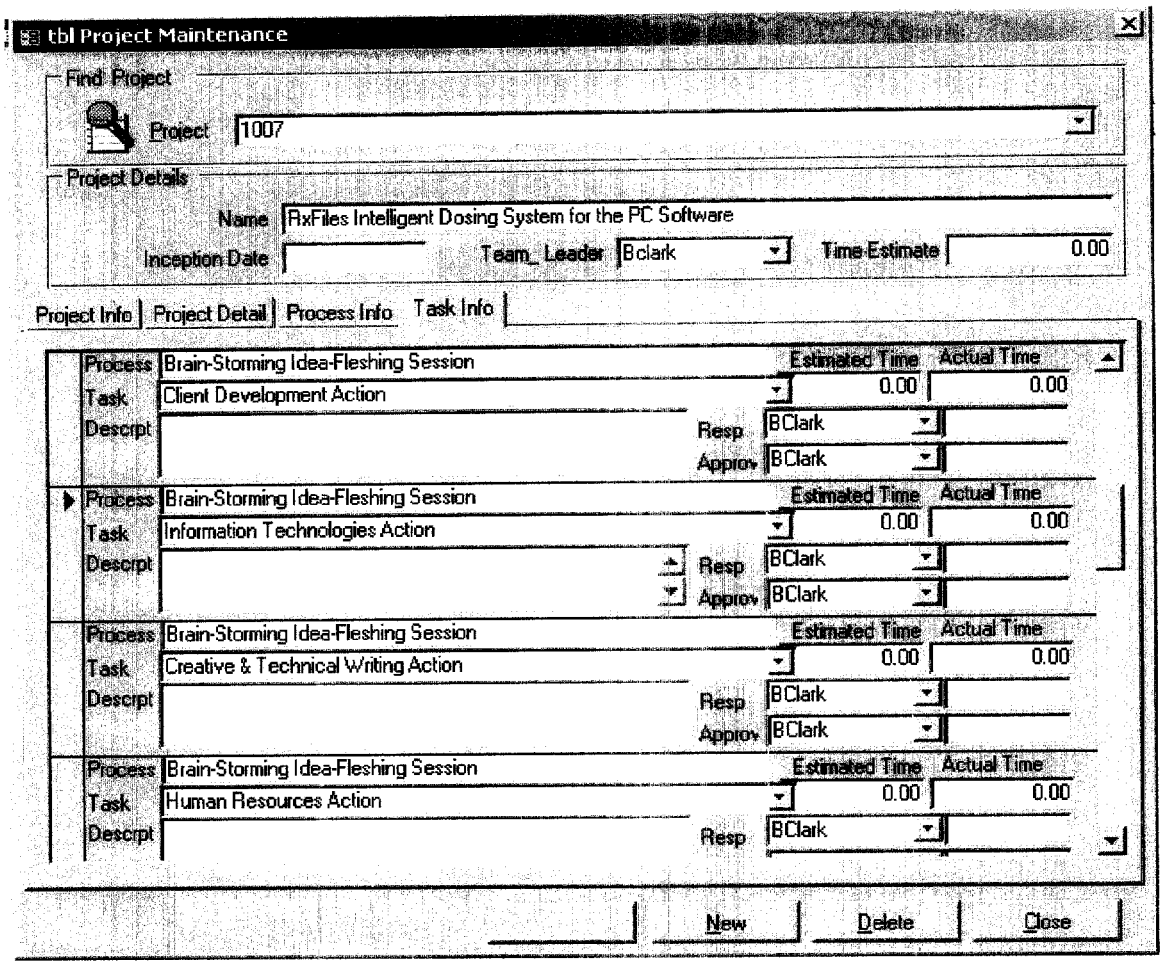
## Introduction

The RxFiles Corporations Project Management System (PMS) was instituted to **register, document and track** the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation **stage completion history** of each enterprise project conceived, ratified and generated by the Firm for Firm wide use. The PMS is comprised of a data repository, graphical user interface and reports generator. The PMS interacts with many other Enterprise wide software application systems to provide command and control capability for all phases of creation, modification and delivery of bona-fide, dynamically evaluated and static tested work product at The RxFiles Corporation.





The **Project Management System (PMS)** contains the Documented Project Detail, Process and Task Information registered and approved for internal release by The RxFiles Corporation, which includes, but is not limited to, testing results for verification and validation of each project version of the Intelligent Dosing System™ (IDS™) Agent Doser Calculators from all Departmental Functionaries.



# SECTION 6
# DESIGN SPECIFICATIONS

(b) (4)

# EXHIBIT 6.1
# Software Requirements Specification and Predetermined Criteria for Acceptance of the Program

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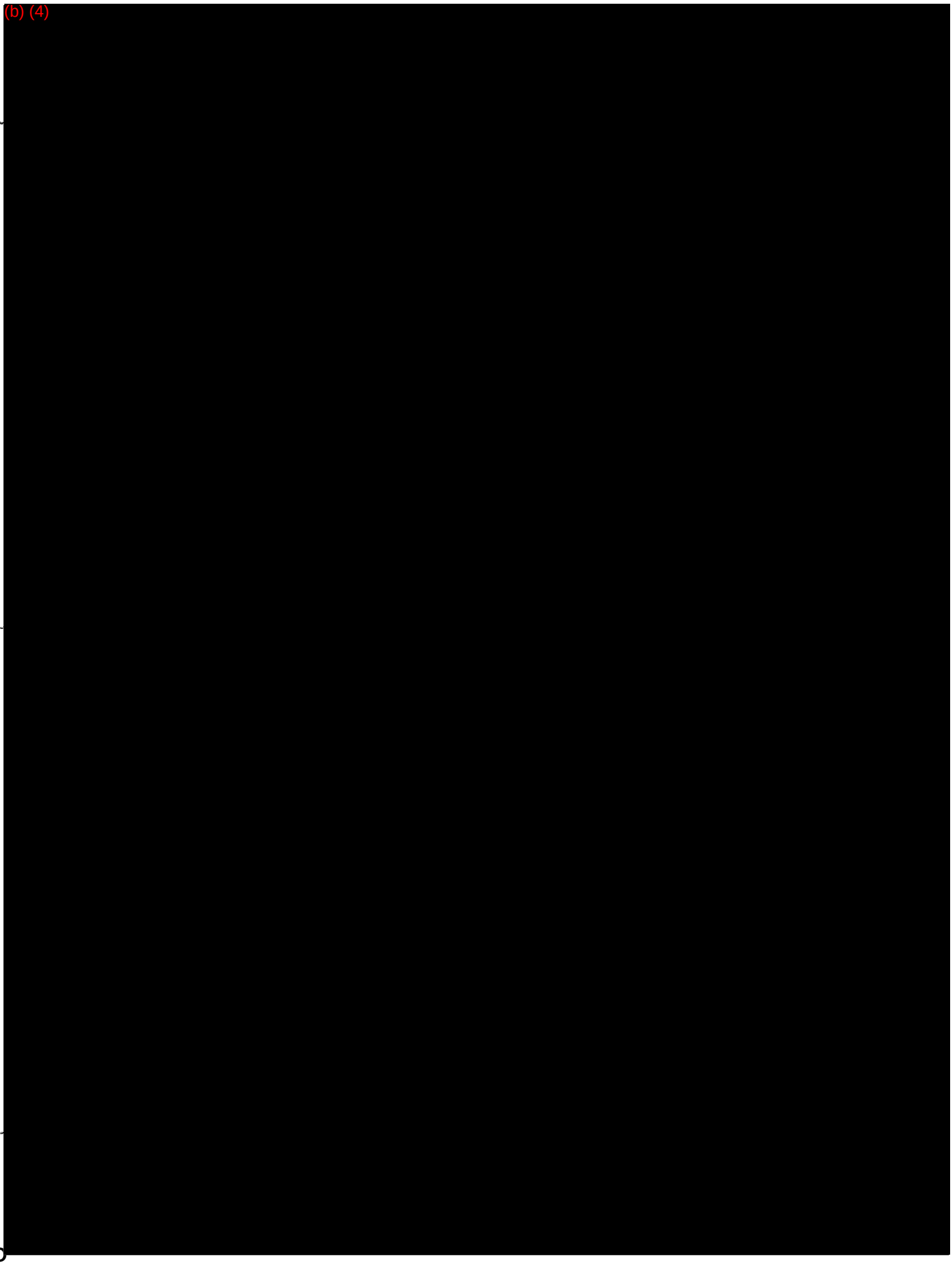
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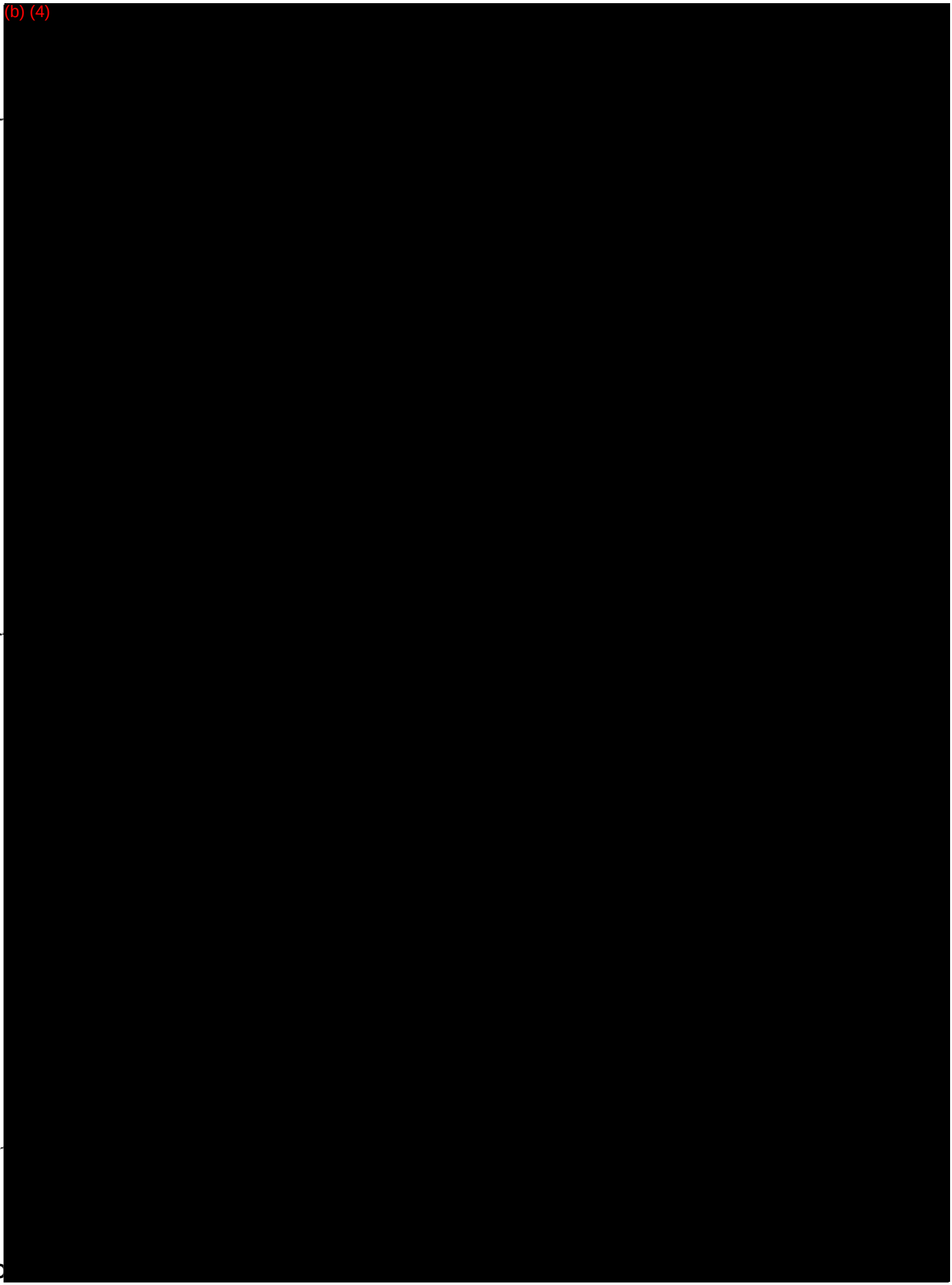
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# EXHIBIT 6.2
# DEVELOPMENT AND PROGRAMMING STANDARDS

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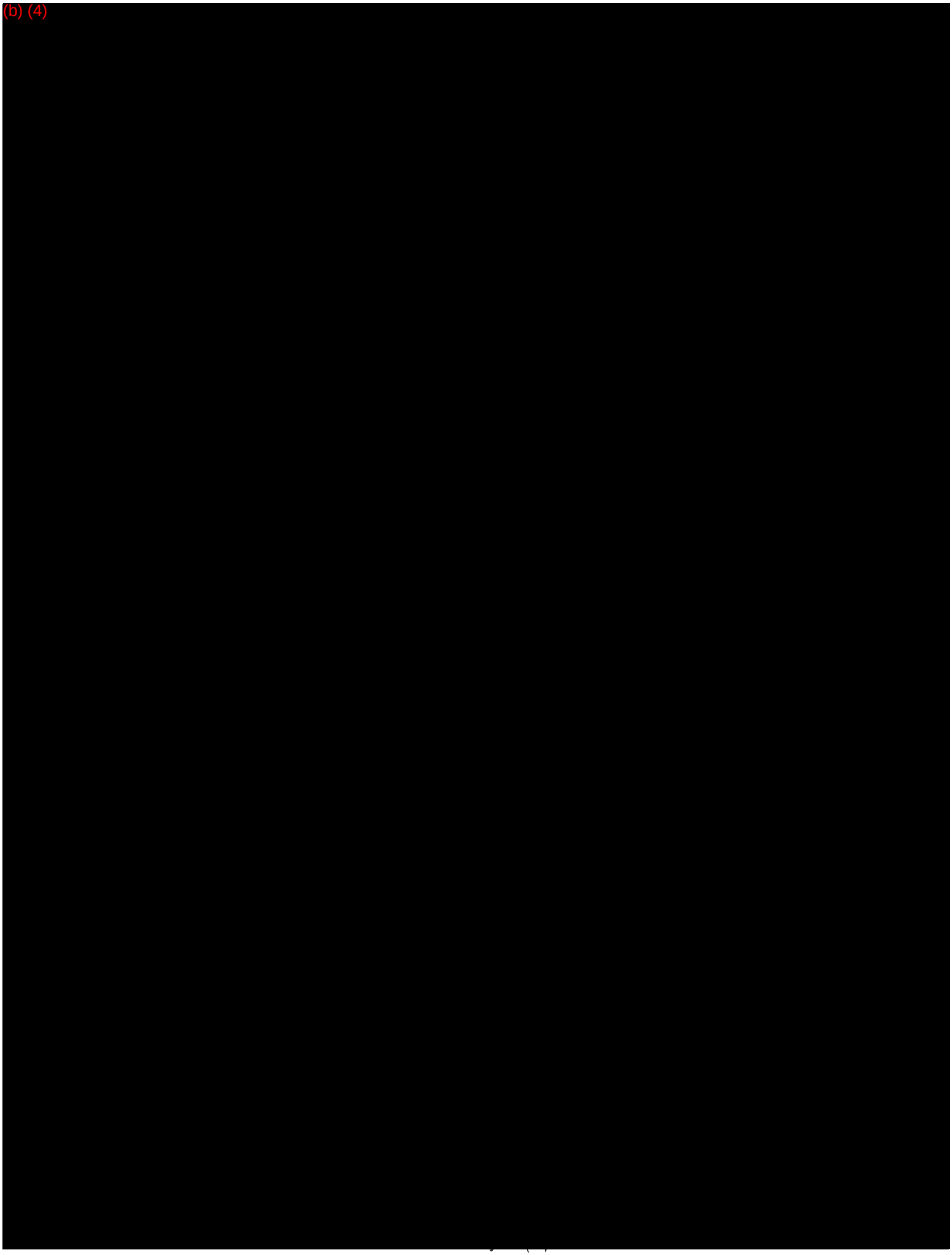
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# EXHIBIT 6.3
# HAZARD ANALYSIS

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# EXHIBIT 6.4
# SYSTEMS DOCUMENTATION

# The RxFiles Corporation Version Management System

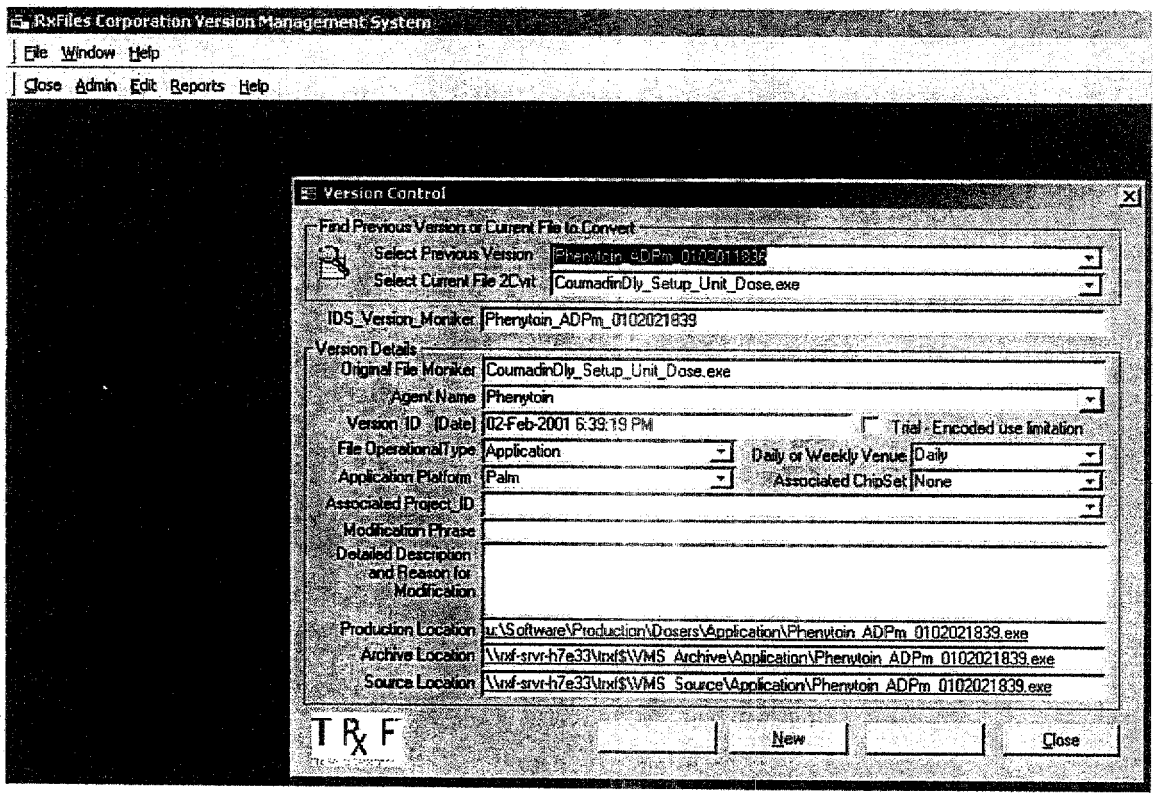
## Focus Statement

The RxFiles Corporation's **Version Management System (VMS)** was instituted to **register, document and track** the Form, Function (including the Designer Formula) and Data **revision history** of each Intelligent Dosing System™ (IDS™) Agent Doser generated by the Firm for general release to the Professional Health Care Industry.

# Overview

**Introduction**

The RxFiles Corporation's **Version Management System (VMS)** was instituted to register, document and track the Form, Function (including the Designer Formula) and Data revision history of each Intelligent Dosing System™ (IDS™) Agent Doser generated by the Firm for general release to the Professional Health Care Industry. The **Version Management System (VMS)** is comprised of a data repository, graphical user interface and reports generator. The **Version Management System (VMS)** interacts with other Enterprise wide software application systems to provide command and control capability for all phases of creation, modification and delivery of bona-fide, dynamically evaluated and static tested work product, in the form of Specific Agent Dosers*.

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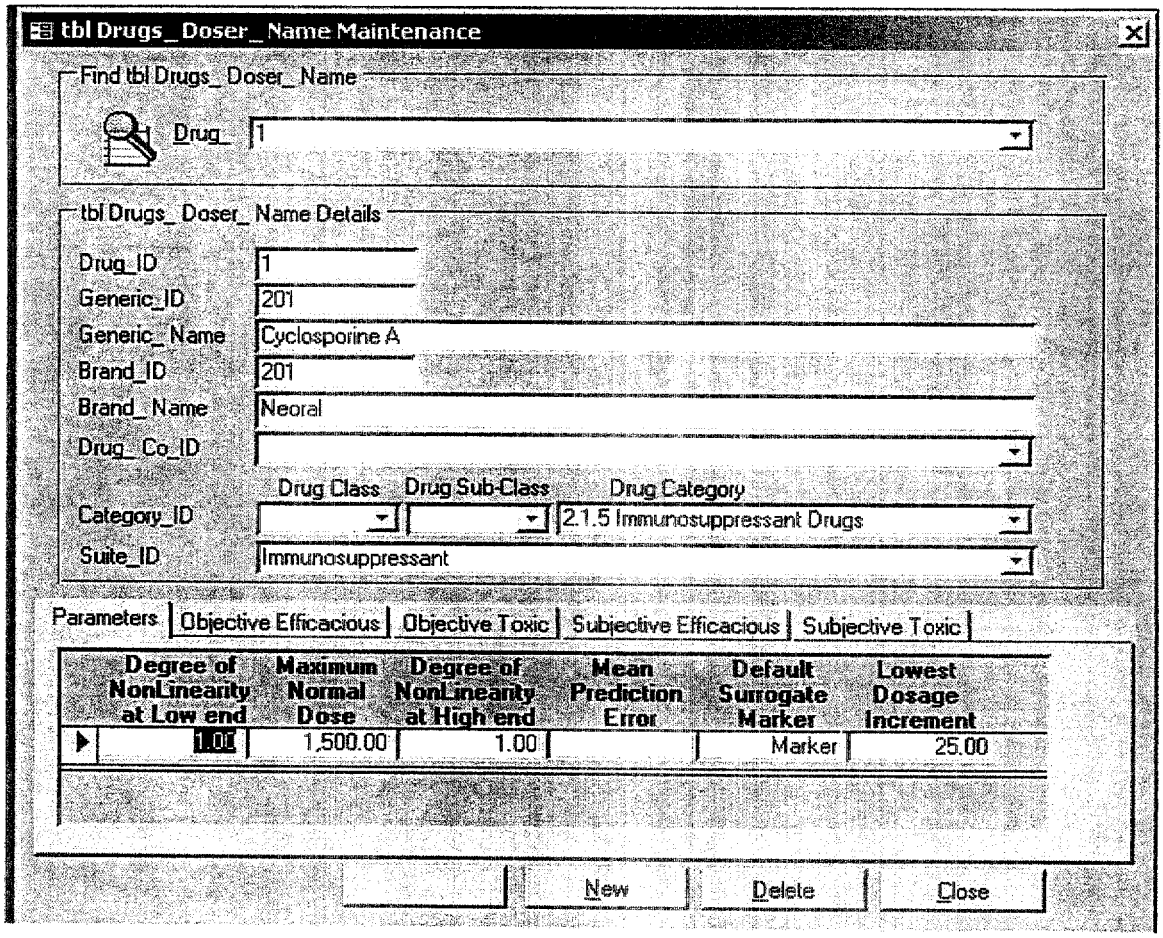
# **Overview**, Continued

The **Version Management System (VMS)** also contains The RxFiles Corporation's entire Formulary, that is, each drug selected and tested for inclusion in a stand alone Agent Doser (IDS™ Calculator Application) or as a selection in a Agents Doser Suite (IDS™ Calculator Application) . All tables, forms and reports labeled with the prefix "tblDrugs" refer to this Formulary and contain the relationships of these drugs to their Drug Classification, Sub-Classification and Category, as well as their individual dosing parameters (specifically Maximum Dose and Minimum Dosing Increment).

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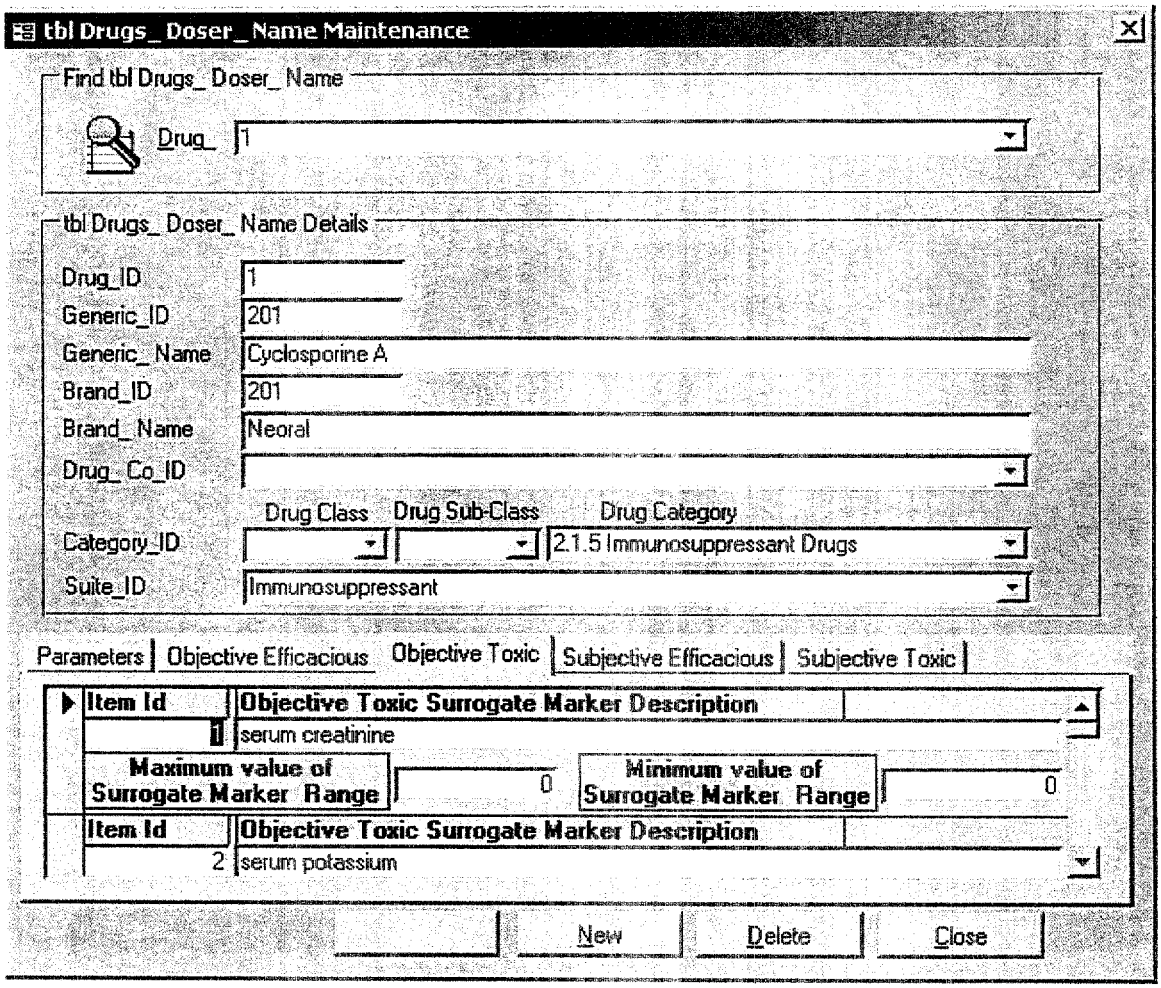
# **Overview**, Continued

The **Version Management System (VMS)** also contains all associated Surrogate Markers with their incident Maximum and Minimum Dose Elements for each Agent in The RxFiles Corporation Formulary.

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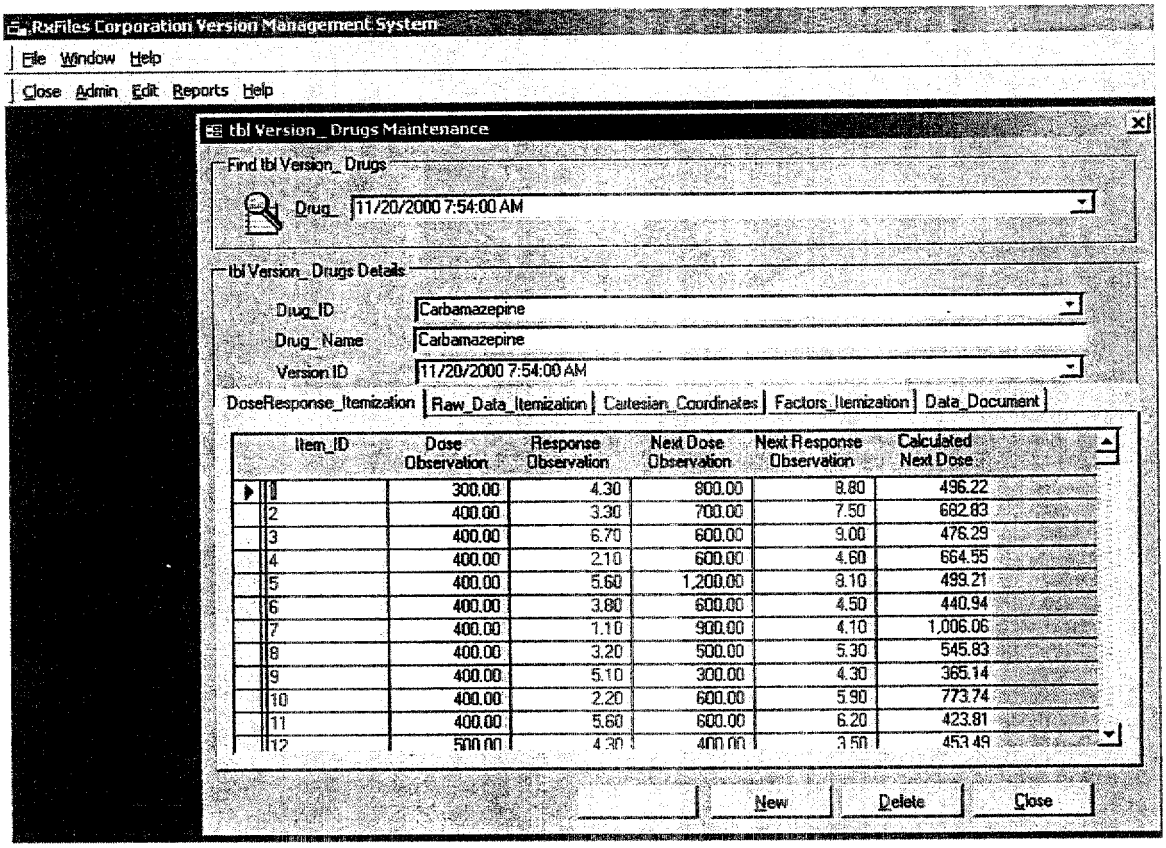
# **Overview**, Continued

The **Version Management System (VMS)** contains the Documented Dose Response, Next Dose Next Response Data Itemization, Raw Patient Data Itemization, Cartesian Plot Coordinates, as well as the calculated Mean, Median, and Standard Deviation calculated Factors Itemization for each Agent Doser registered and approved for general release by The RxFiles Corporation.




| Item_ID | Dose Observation | Response Observation | Next Dose Observation | Next Response Observation | Calculated Next Dose |
|---|---|---|---|---|---|
| 1 | 300.00 | 4.30 | 900.00 | 8.80 | 496.22 |
| 2 | 400.00 | 3.30 | 700.00 | 7.50 | 682.83 |
| 3 | 400.00 | 6.70 | 600.00 | 9.00 | 476.29 |
| 4 | 400.00 | 2.10 | 600.00 | 4.60 | 664.55 |
| 5 | 400.00 | 5.60 | 1,200.00 | 8.10 | 499.21 |
| 6 | 400.00 | 3.80 | 600.00 | 4.50 | 440.94 |
| 7 | 400.00 | 1.10 | 900.00 | 4.10 | 1,006.06 |
| 8 | 400.00 | 3.20 | 500.00 | 5.30 | 545.83 |
| 9 | 400.00 | 5.10 | 300.00 | 4.30 | 365.14 |
| 10 | 400.00 | 2.20 | 600.00 | 5.90 | 773.74 |
| 11 | 400.00 | 5.60 | 600.00 | 6.20 | 423.81 |
| 12 | 500.00 | 4.30 | 400.00 | 3.50 | 453.49 |

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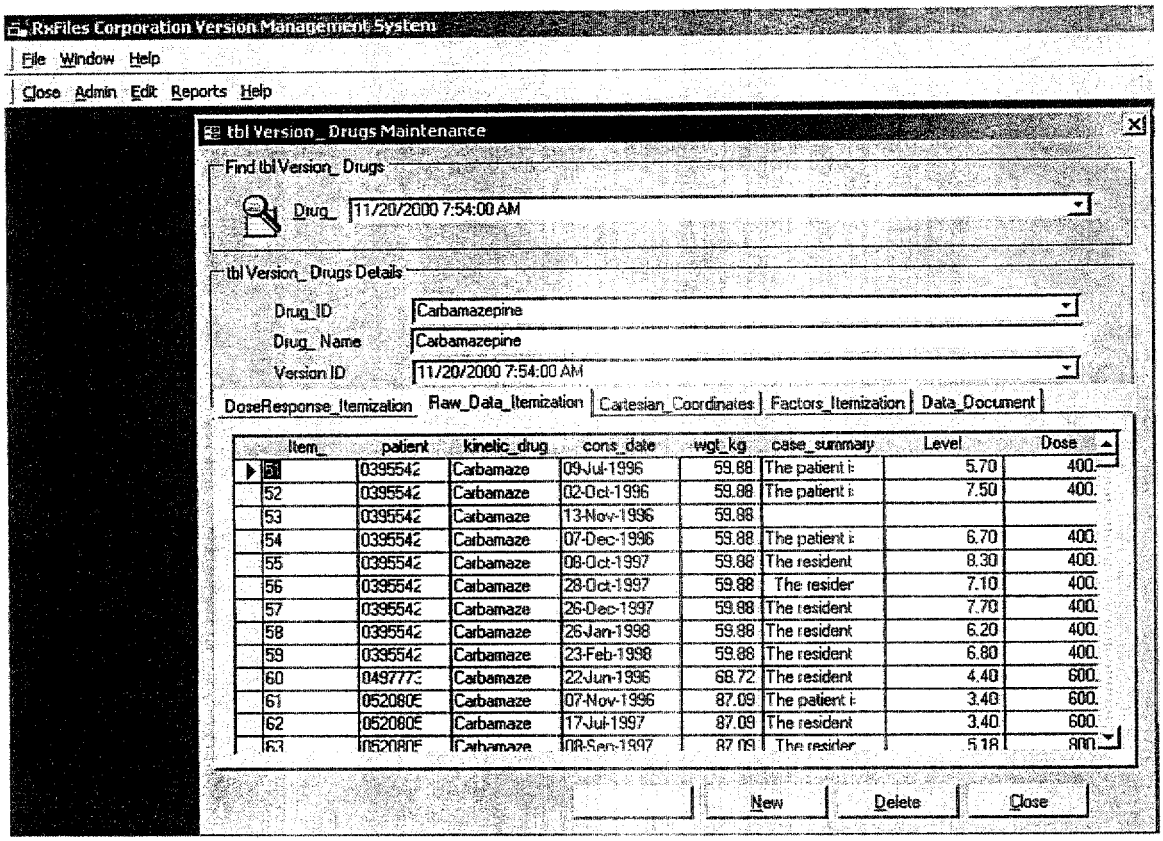
# **Overview**, Continued

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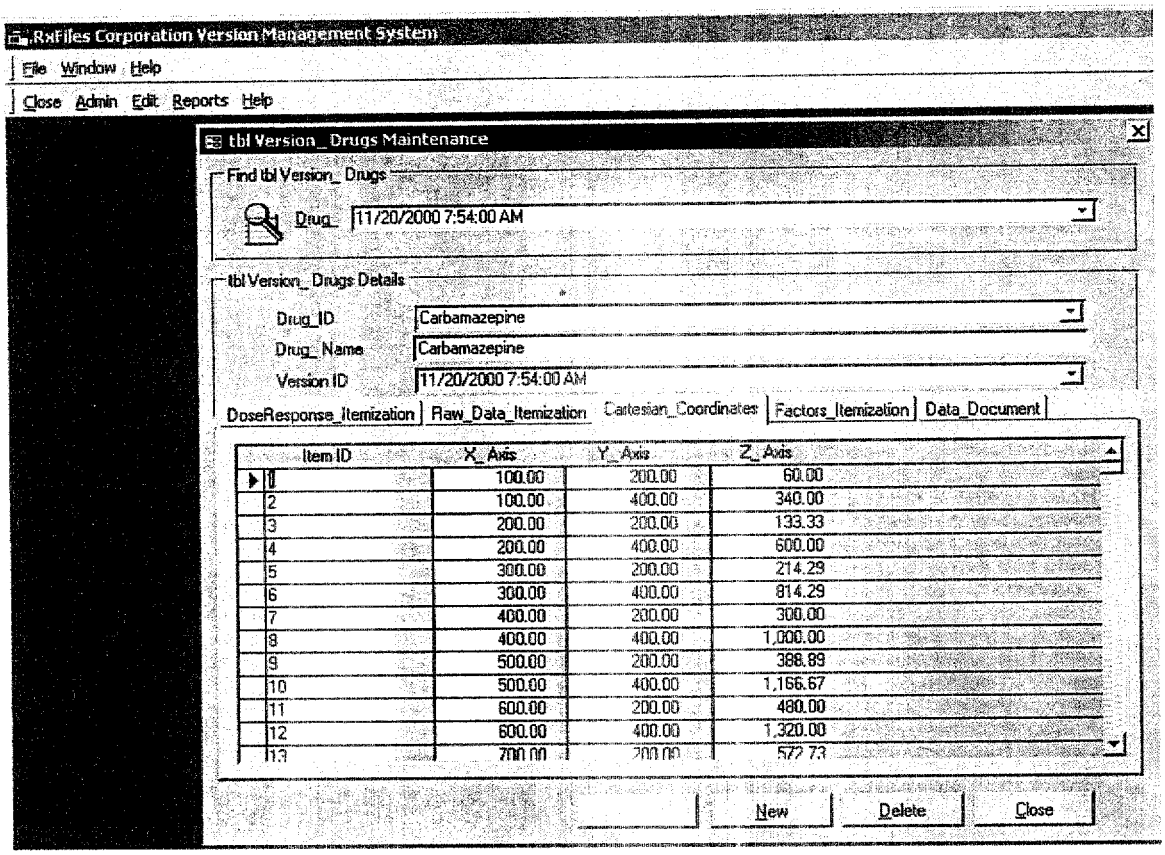
# **Overview**, Continued

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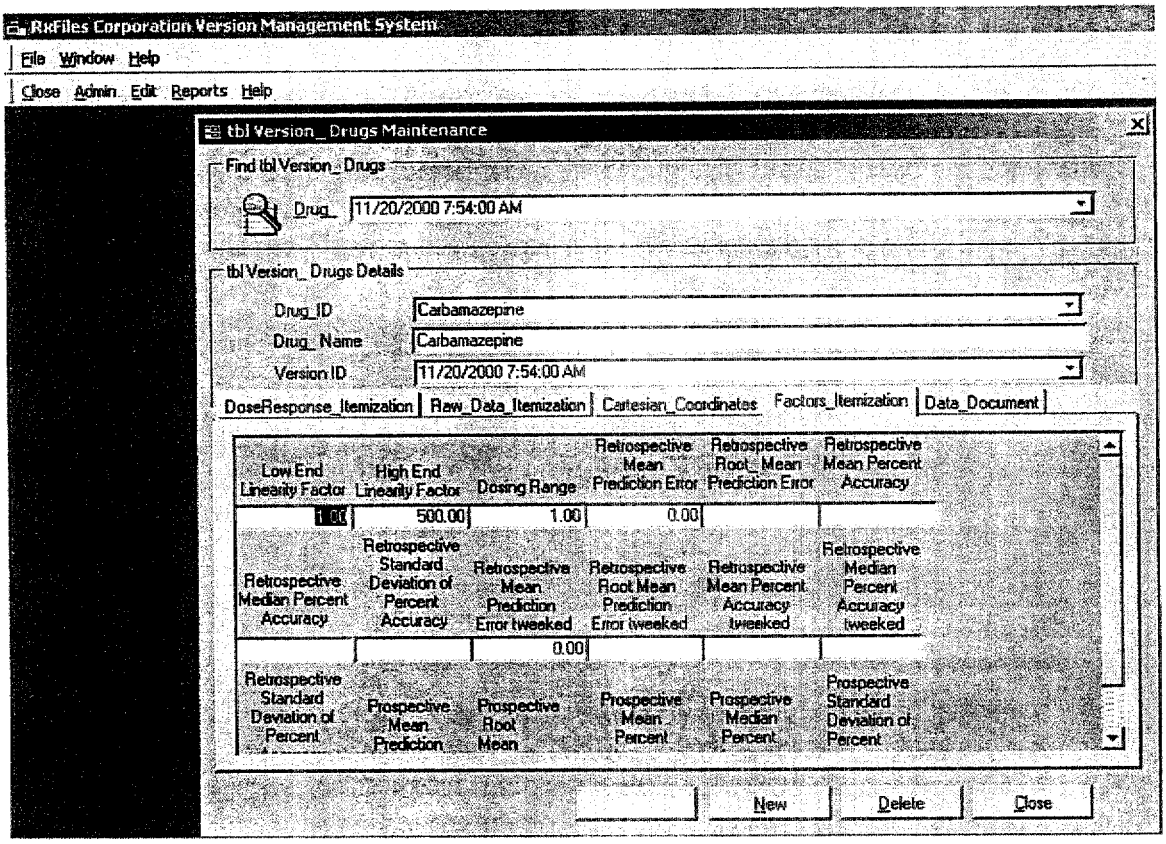
# **Overview**, Continued

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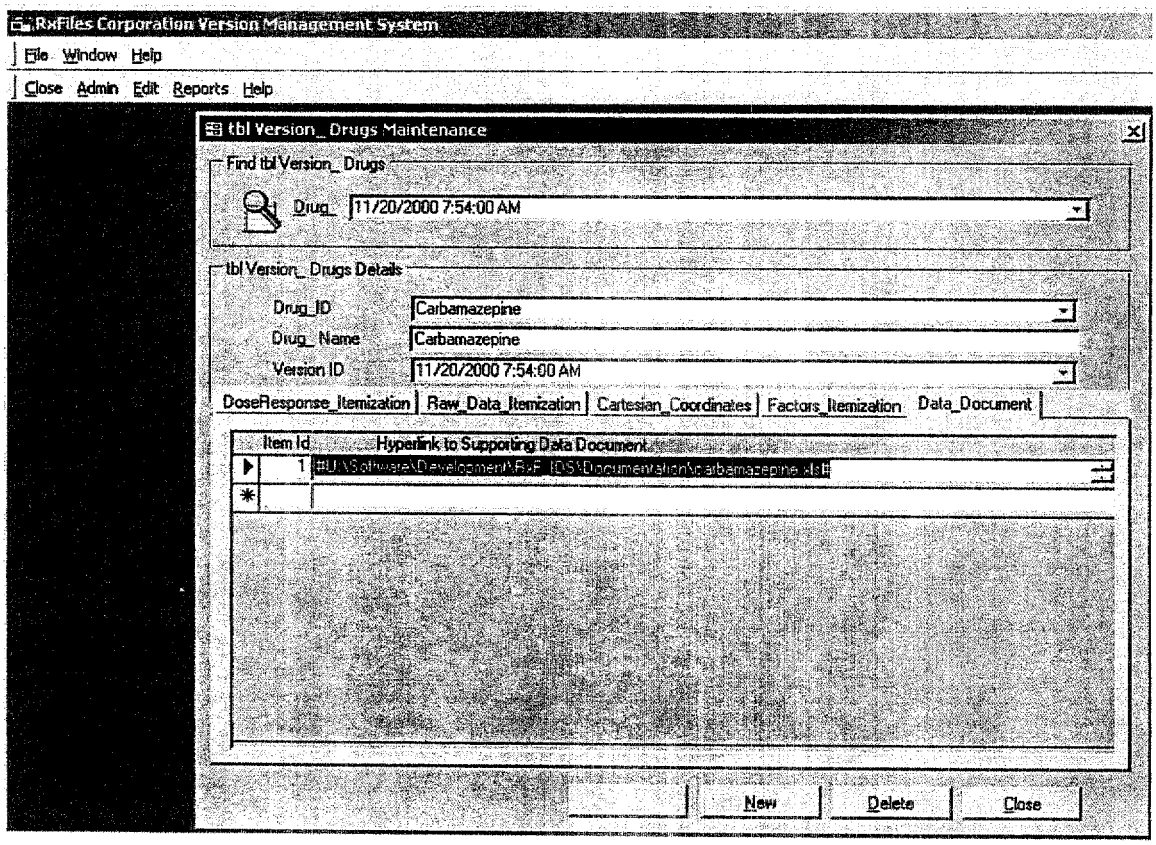
# **Overview**, Continued

Each document of supporting evidence which substantiates the dosing accuracy of each Registered Agent Doser is also itemized and identified by a URL path hyperlink to the documents actual location in our document repository. (For futher discussion, see all documentation detailing The RxFiles Corporation's Document Management System (DMS)).

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# **Overview**, Continued

The Version Management System also contains the itemized Validation and Verification methodologies and protocols, together with Test Results, Testor Identification and Testor Notes regarding an Agent Doser's idiosyncracies and anomalies discovered during testing.

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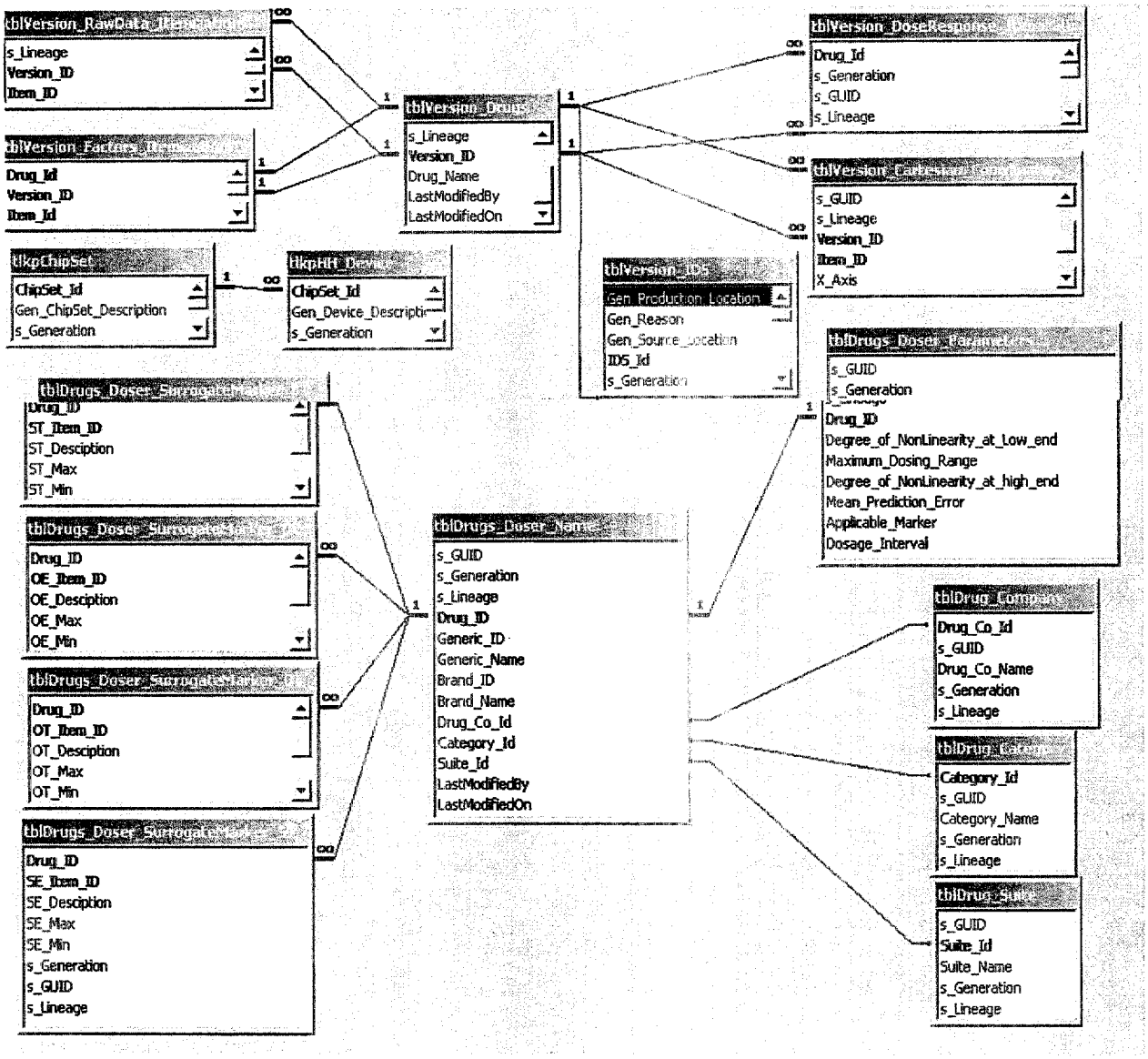
# **Overview**, Continued

## Version Management System Entitity Relationship Diagram



# The RxFiles Corporation
# Project Management System

## Focus Statement

The RxFiles Corporation's **Project Management System (PMS)** was instituted to **register, document and track** the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation **stage completion history** of each enterprise project conceived, ratified and generated by the Firm for Firm wide use.

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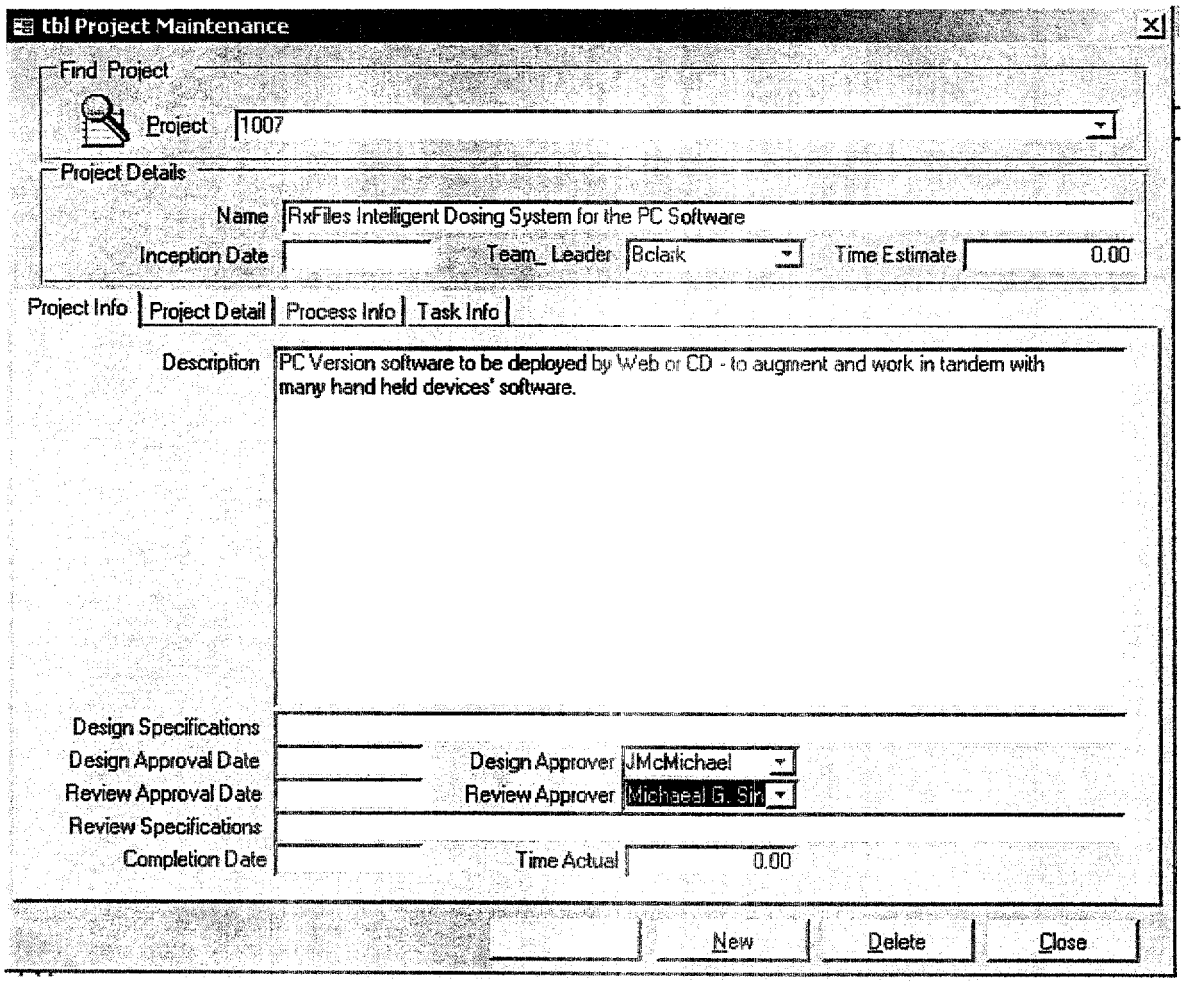


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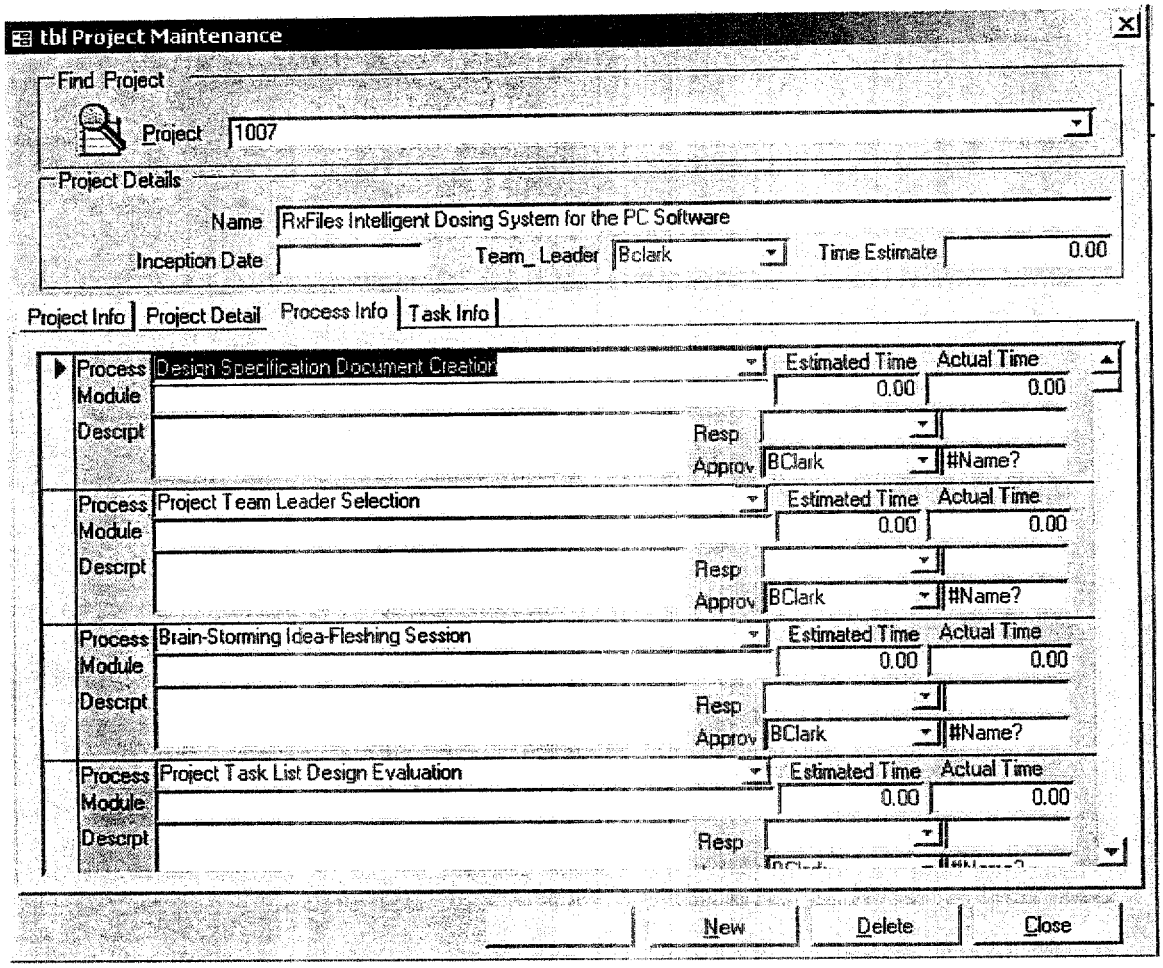
# **Overview**, Continued

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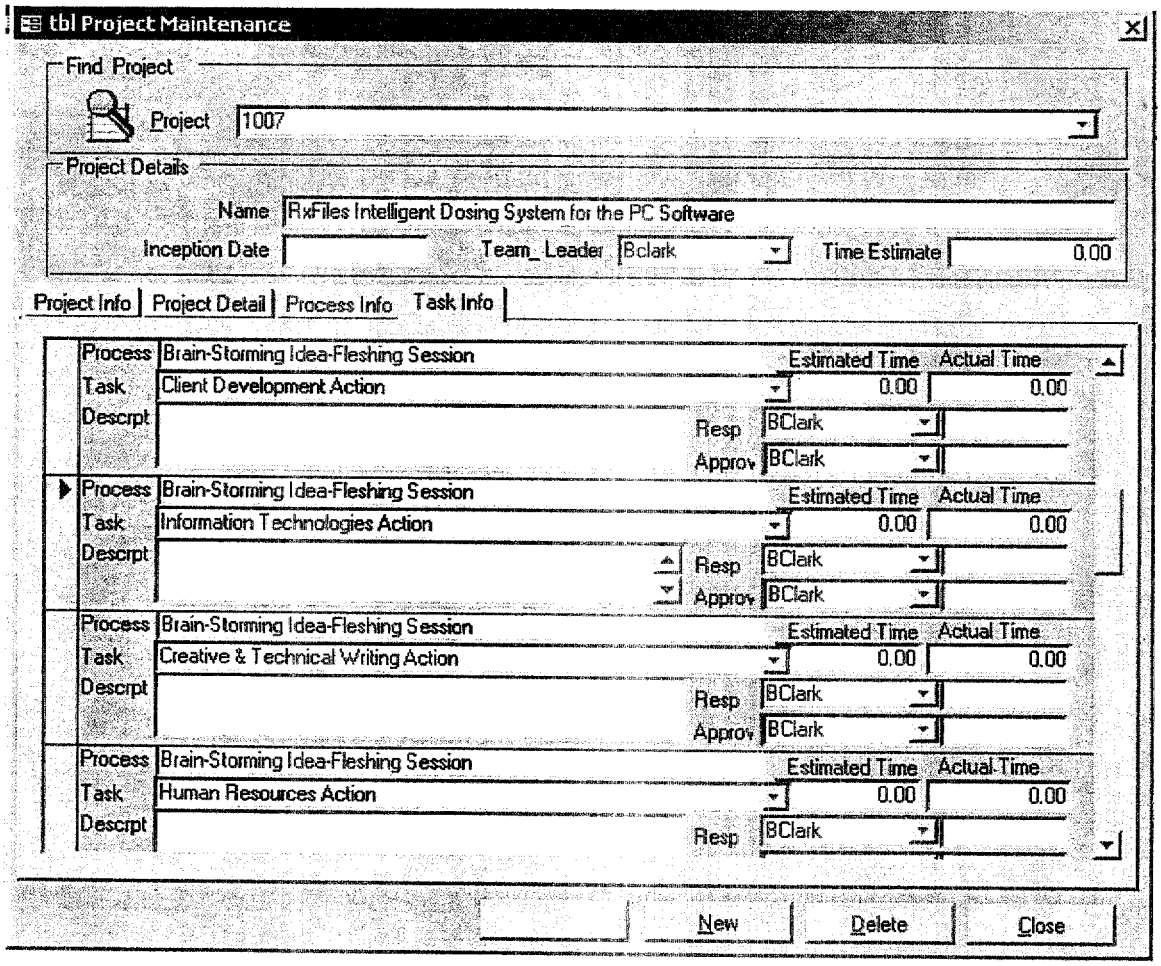
# **Overview**, Continued

The **Project Management System (PMS)** contains the Documented Project Detail, Process and Task Information registered and approved for internal release by The RxFiles Corporation, which includes, but is not limited to, testing results for verification and validation of each project version of the Intelligent Dosing System™ (IDS™) Agent Doser Calculators from all Departmental Functionaries.

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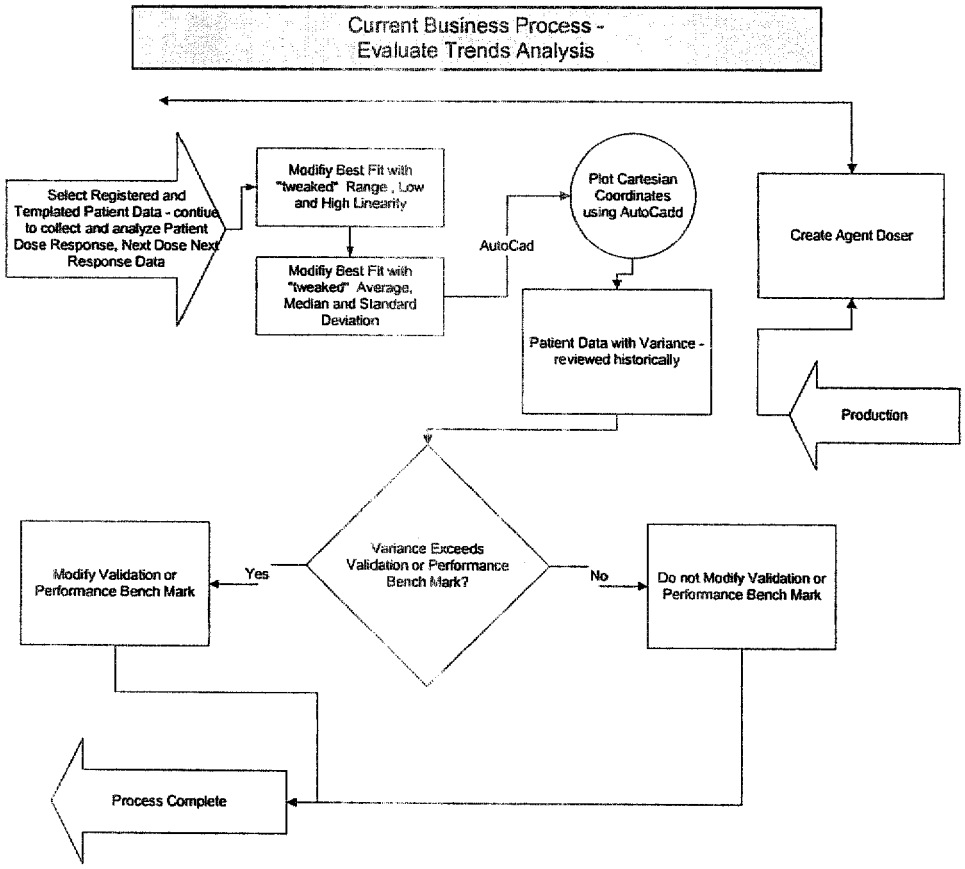
# Activity Requirements - Evaluate Trends Analysis

**Overview**

The Evaluate Trends Analysis process allows the Information Services Interface Personnel the ability to review periodically Agent Doser Requests and the incident Patient Data produced therefore. This protocal, which is part of the overall Quality Assurance Process, provides a historical, accumulative perspective regarding all data used to produce validity and bench mark items for present and future Agent Dosers. The current business process is very procedural and user intensive. Most of the actions required by the user are to be automated. This activity is considered to be a Key Performance Indicator of this project. See also: Evaluate Work-In-Progress/Work-in-route.

**Current Business Process - Evaluate Trends Analysis**

The current business process for Evaluate Trends Analysis is shown below.

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# Activity Requirements - Reconcile Best Fit with Patient Data, Continued

**Entity/ Relationships - Reconcile Best Fit with Patient Data**

The relationships in the entity relationship diagram (see appendix) are explained below. Please note these dependencies apply only to these entities in the context of Reconcile Best Fit with Patient Data.

Best Fit with Patient Data is a way of representationally modeling the various elements of the dose response, next dose next response curve incident to a Doser Agent Item produced during the Production of an Agent Doser. It was once necessary to compare various arbitrary selections of low and high degree of linearity for a given Agent in order to reconcile a Best Fit with Patient Data. Our quality assurance program has eliminated the necessity for the inclusion of these elements.

Over the course of providing dose response, next dose next response relationships for our initial Agent Dosers we recognized the fact that we could substitute the numeral one (1) for the Degree of NonLinearity at the Low end or for the Degree of NonLinearity at the High end. All that is necessary to perform a best-fit analysis are the Cartesian coordinates along the customary increments of the known range from zero (0) to the Maximum Dose for that Agent. Any variance that exceeds the customary validation or performance benchmark is used to modify the performance benchmark. Otherwise the benchmark is retained as is. A crosscheck of the registered Best Fit with Patient Data is performed by Information Systems Interfacing Personnel and should reveal any anomalous situations. However, the following observations still apply, to-wit:

1. Typically an increase in dose will result in an increase in therapeutic efficacy.
2. Typically a decrease in dose will result in a decrease in toxicity.
3. The degree of increase in level is somewhat dependant on the degree of increase in dose.
4. Other factors, external to the dose-response curve relationship, act on the subject to also alter the dose/marker relationship.
5. When dosing a patient, the subject can only experience sub-therapeutic response, optimal therapy, or toxicity (although optimal therapy may involve subjecting the patient to some toxicity.
6. When external forces (other than the dose/response curve) act upon a subject, adjustments need to be made for them.

# The RxFiles Corporation Document Management System

## Focus Statement

The RxFiles Corporation's **Document Management System (DMS)** was instituted to **register and track** White Papers, Systems Supporting Documentation, Research Papers and Associated written errata, together with their individual **revision history,** generated by the Firm for general release to the Professional Health Care Industry.

# Overview

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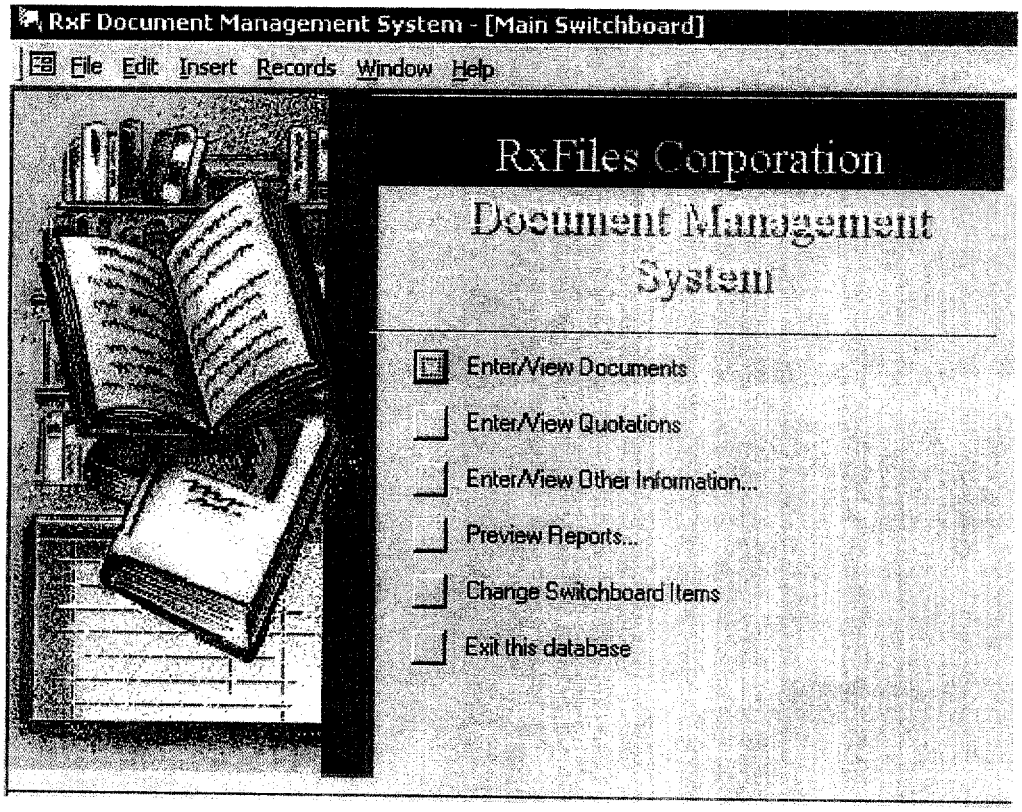


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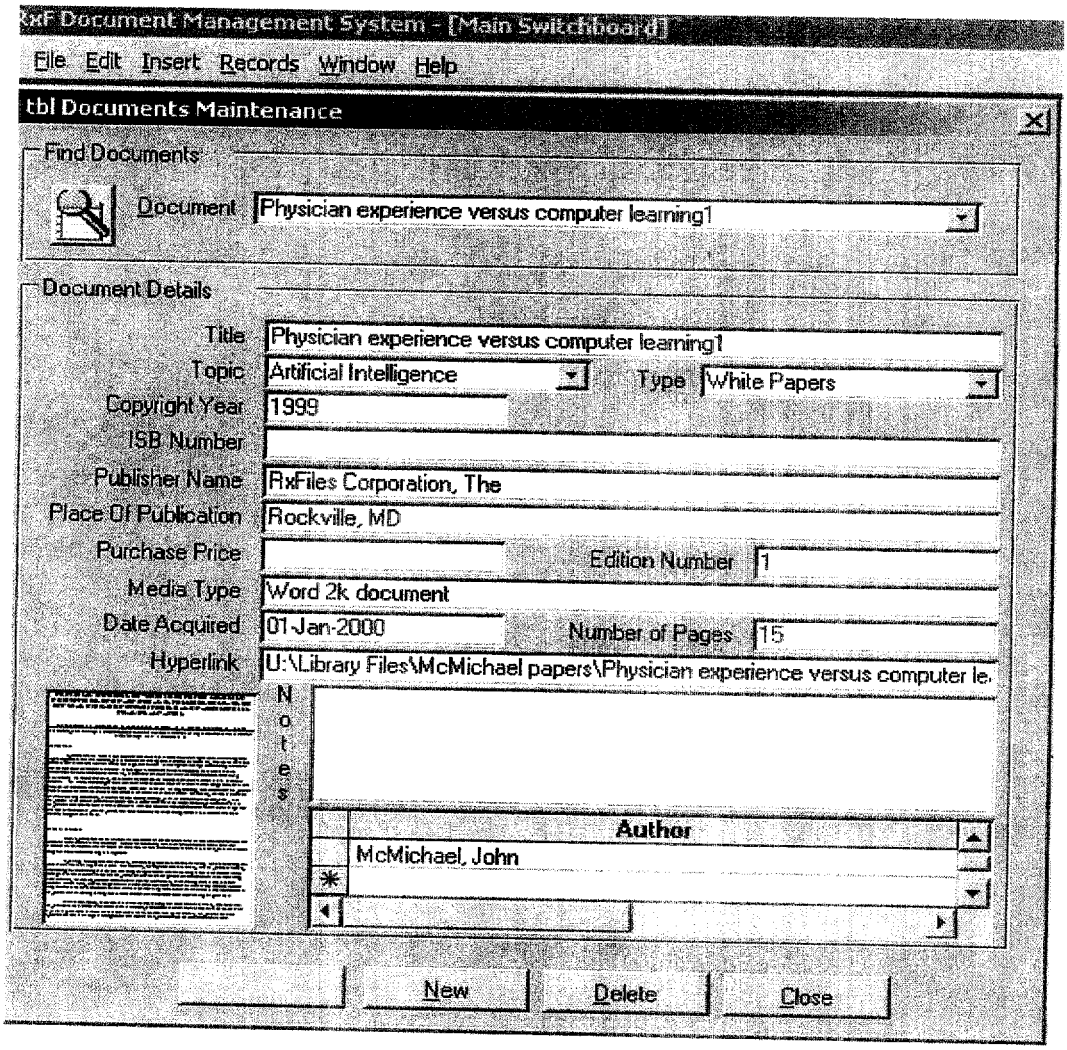
# **Overview**, Continued

The Document Management System affords a custom find feature to allow browsing of system-wide documentation for the standpoint of Document Topic, Document Type, as well as by Document Title and affilliation with the Document Author or Authors. The Documents Maintenance form affords a look a the Edition History, Media Type, Place of Publication, Date Acquired, together with a hyperlink to the document itself. A thumnail rendering of the cover page of the document is included as well as Copyright Date, Acquisition Date and Publisher Name. Any Notes, Quotes or Editorial Comments are registered here as well.

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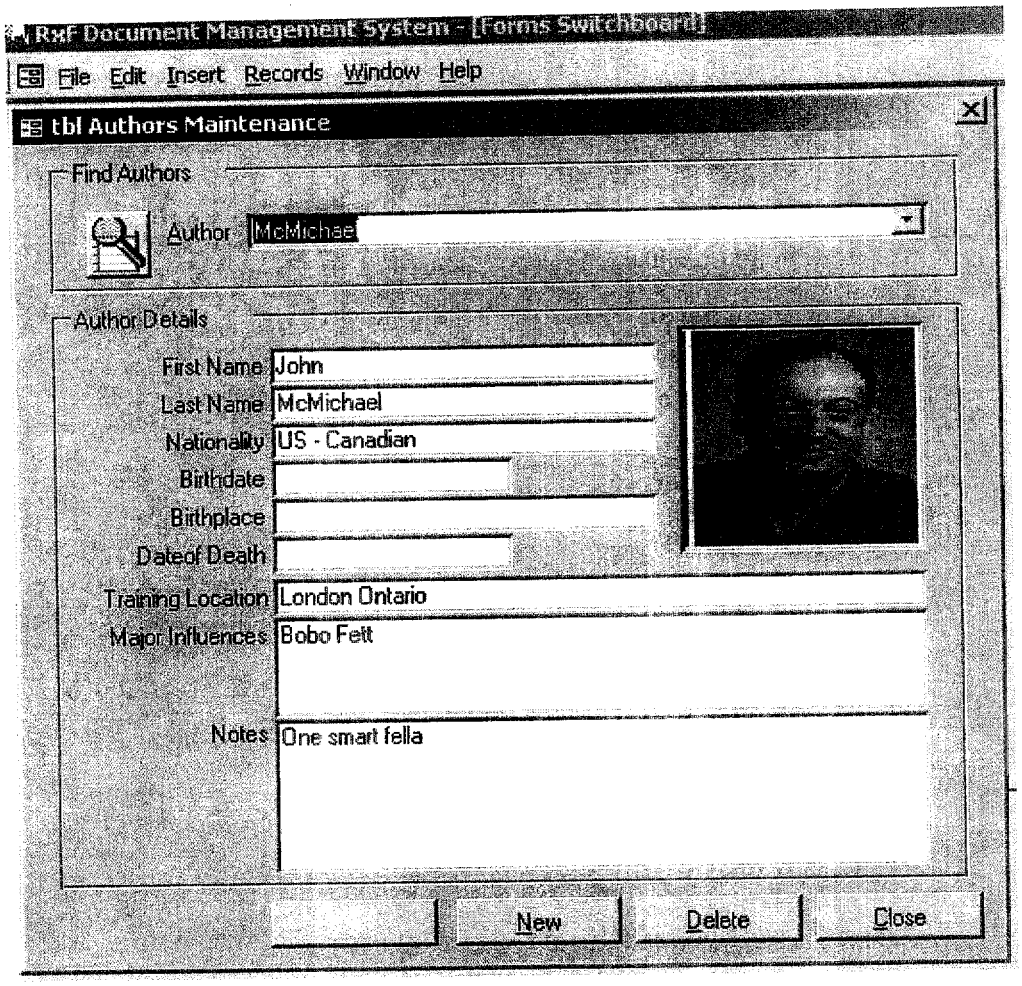
# Overview, Continued

The Document Management System directs the itemization and cross-correlation of Authors with Documents. The Authors Maintenance form allows users to document relevant information regarding each author associated with a document.

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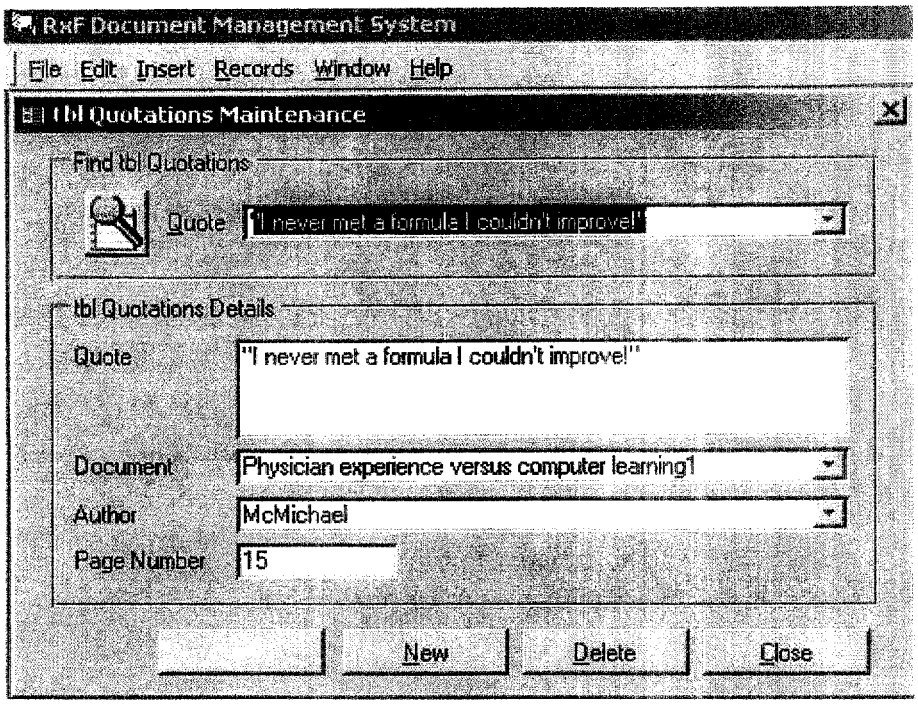
# **Overview**, Continued

The Document Management System directs the itemization and cross-correlation of Authors with Documents. The Authors Maintenance form allows users to document relevant information regarding each author associated with a document.



# EXHIBIT 6.5
# HARDWARE TO BE USED

(b) (4)

[redacted]

F

# EXHIBIT 6.6
# PARAMETERS FOR PROGRAM

(b) (4)

[redacted]

(b) (4)

[redacted]

# EXHIBIT 6.7
# LOGIC

S.6 Logic

(b) (4)

[redacted]

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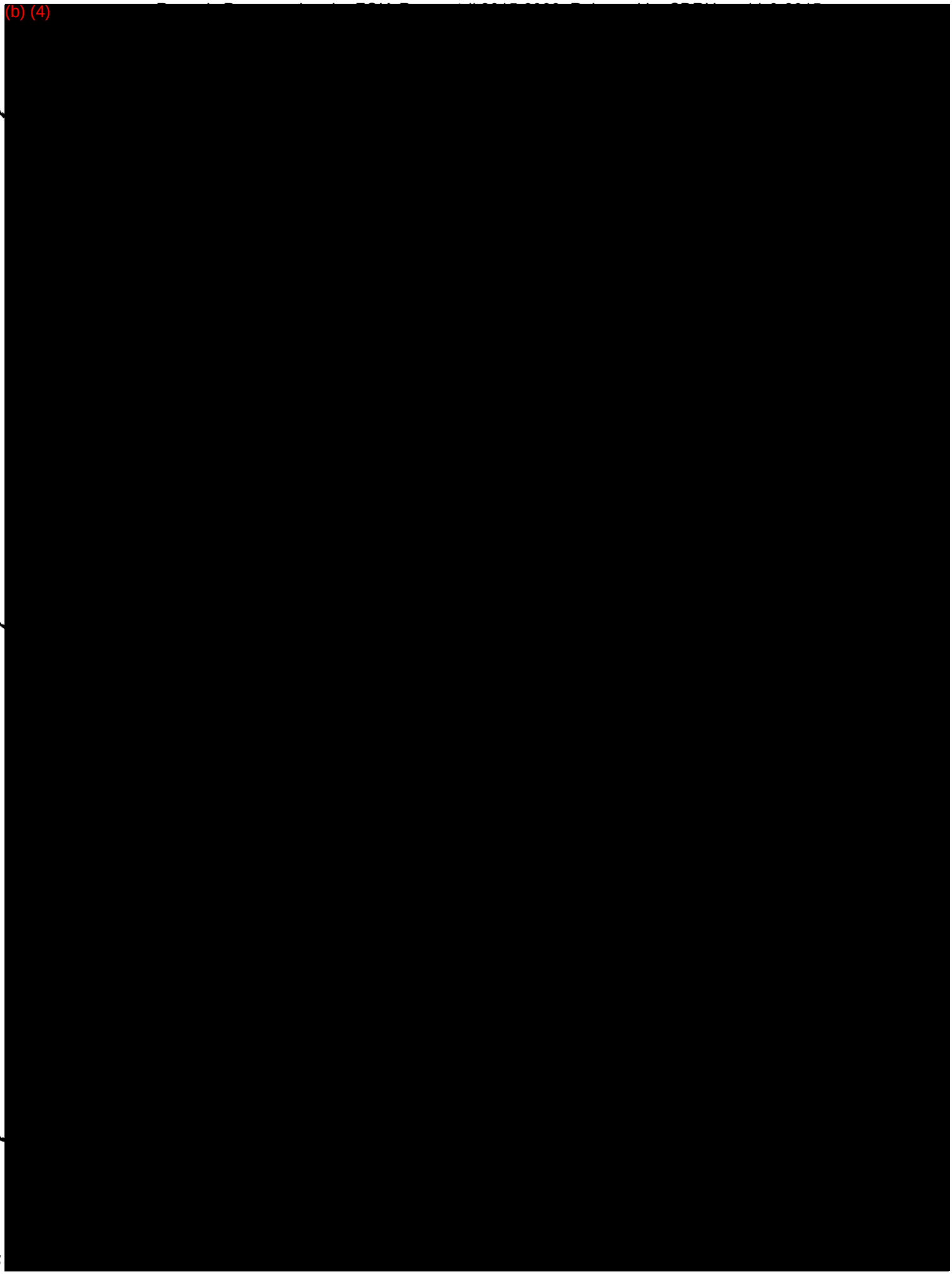
(b) (4)



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FO

# EXHIBIT 6.8
# DATA STRUCTURES AND DATA FLOW DIAGRAMS

(b) (4)

[redacted]

(b) (4)

[redacted]

# EXHIBIT 6.9
# DESCRIPTION OF VARIABLES

3.6 Description of Variables and where they are used.

(b) (4)

[redacted]

(b) (4)

[redacted]

# Activity Requirements - Evaluate Implementation of Agent to be Dosed, Continued

**Generic Formulae for Any Agent Doser – Stochastic Open Loop**

The formulae for the stochastic open loop which mitigates the various factors which can influence a subject's Marker is as follows:

$$\text{New Dose} = \text{Dose} - \left[\frac{\text{Change in level function}}{\text{Degree of non-linearity over the dosing range function}}\right] \times \text{Dose} + \text{some individualized amount based on individuals response to dosing}$$

$$((0.2 \times CD) \times ((d - e) / abs(d))) / 1.3 \wedge (CD/Range)$$

Or represented as:

$$\frac{((0.2 \times CD) \times ((d - e) / abs(d)))}{1.3 \wedge (CD/Range)}$$

CD = Current Dose
DL = Desired Level
PL = Previous Level
d = CL – PL
e = DL – PL

*Continued on next page*

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# EXHIBIT 6.10
# SUPPORTING SOFTWARE

(b) (4)

# EXHIBIT 6.11
# SECURITY MEASURES

(b) (4)



347

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

# SECTION 7
# ARCHITECTURE DESIGN CHART

# EXHIBIT 7.1
# ARCHITECTURE DESIGN CHART

(b) (4)

[redacted]

# SECTION 8
# TRACEABILITY ANALYSIS

# SECTION 8: TRACEABILITY ANALYSIS

**8.1 Traceability Analysis:** Reference Exhibit 8.1

# EXHIBIT 8.1
# TRACEABILITY ANALYSIS

# The RxFiles Corporation
# Project Management System

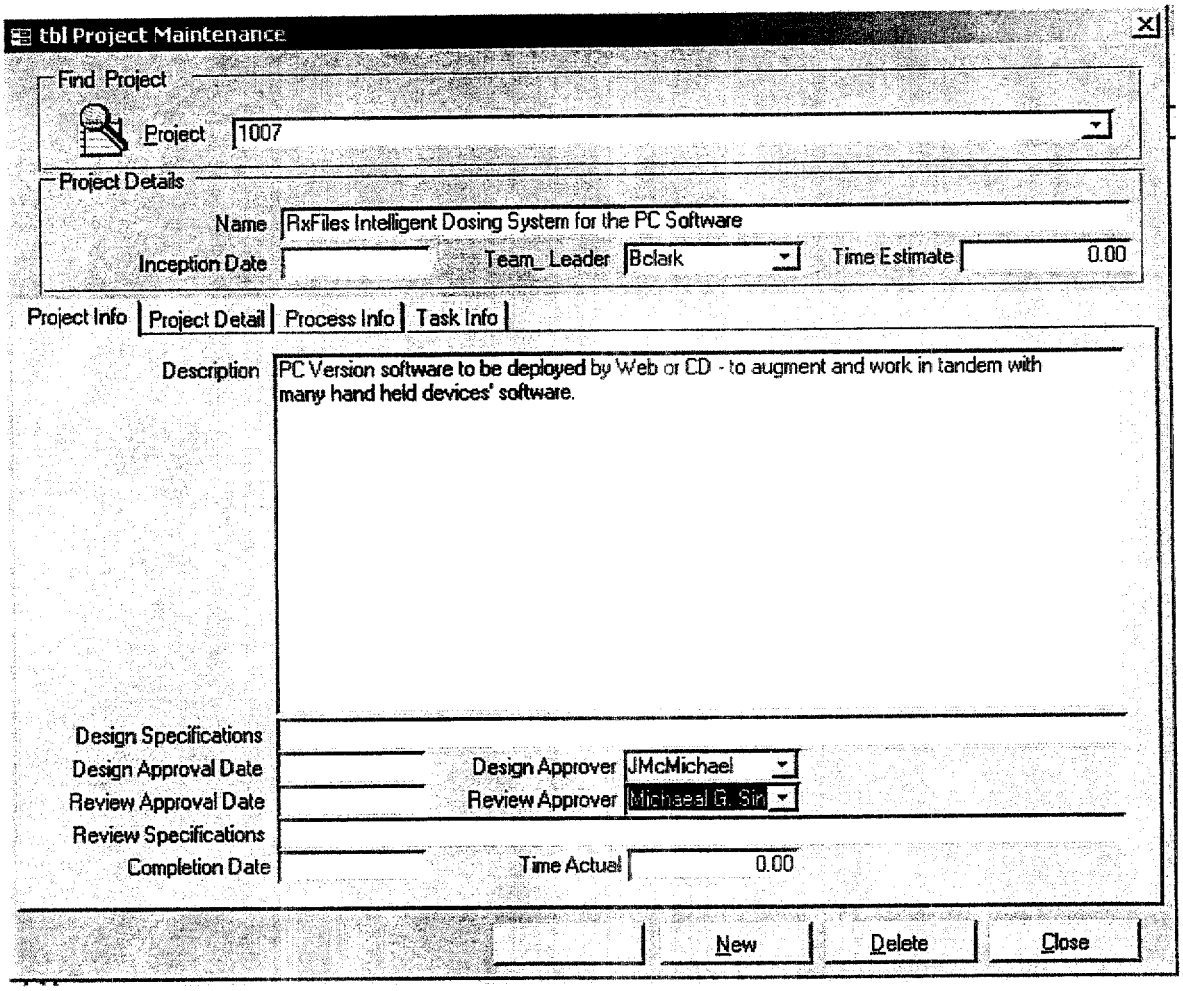
## Focus Statement

The RxFiles Corporation's **Project Management System (PMS)** was instituted to **register, document and track** the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation **stage completion history** of each enterprise project conceived, ratified and generated by the Firm for Firm wide use.

# Overview

**Introduction**

The RxFiles Corporation's **Project Management System (PMS)** was instituted to register, document and track the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation stage completion history of each enterprise project conceived, ratified and generated by the Firm for Firm wide use. The **Project Management System (PMS)** is comprised of a data repository, graphical user interface and reports generator. The **Project Management System (PMS)** interacts with many other Enterprise wide software application systems to provide command and control capability for all phases of creation, modification and delivery of bona-fide, dynamically evaluated and static tested work product at The RxFiles Corporation.

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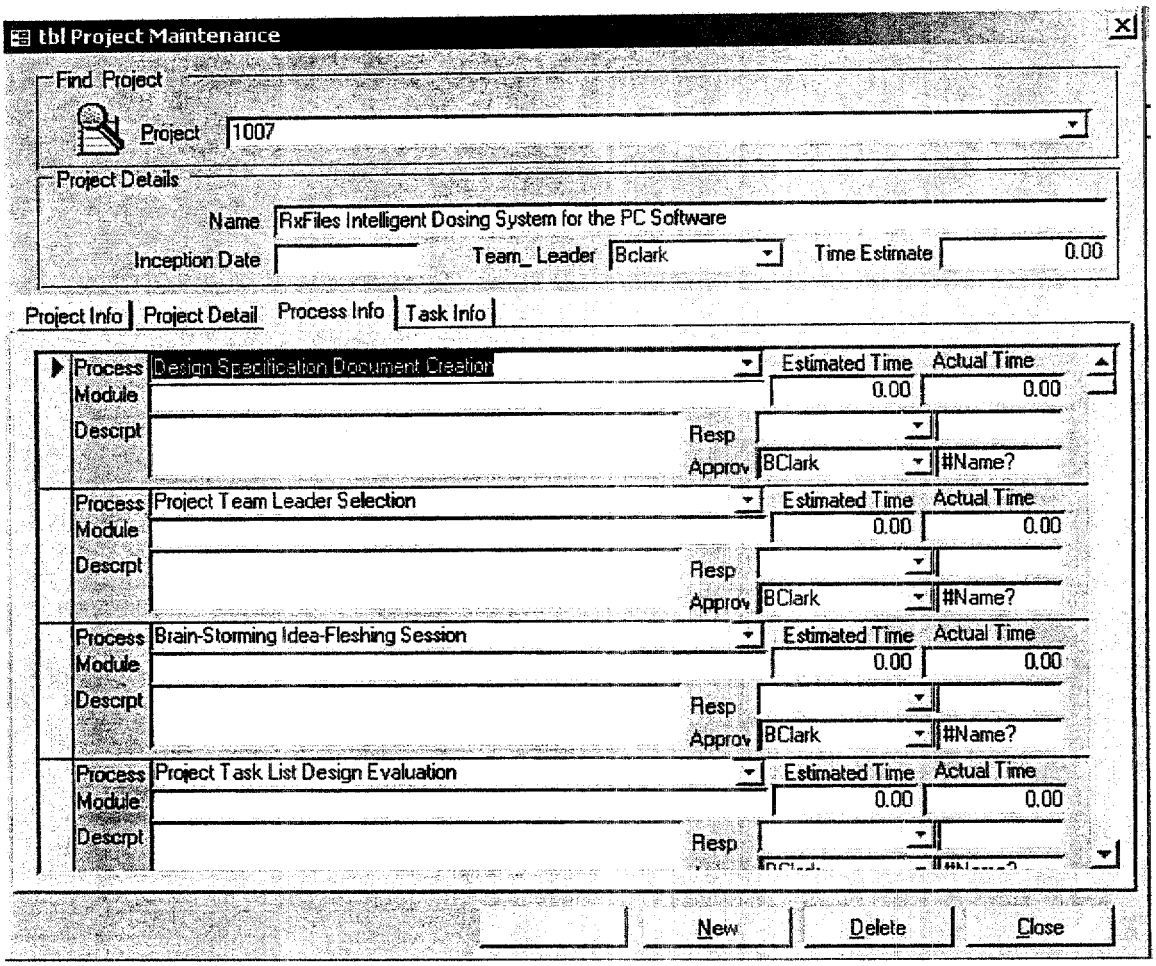
# **Overview**, Continued

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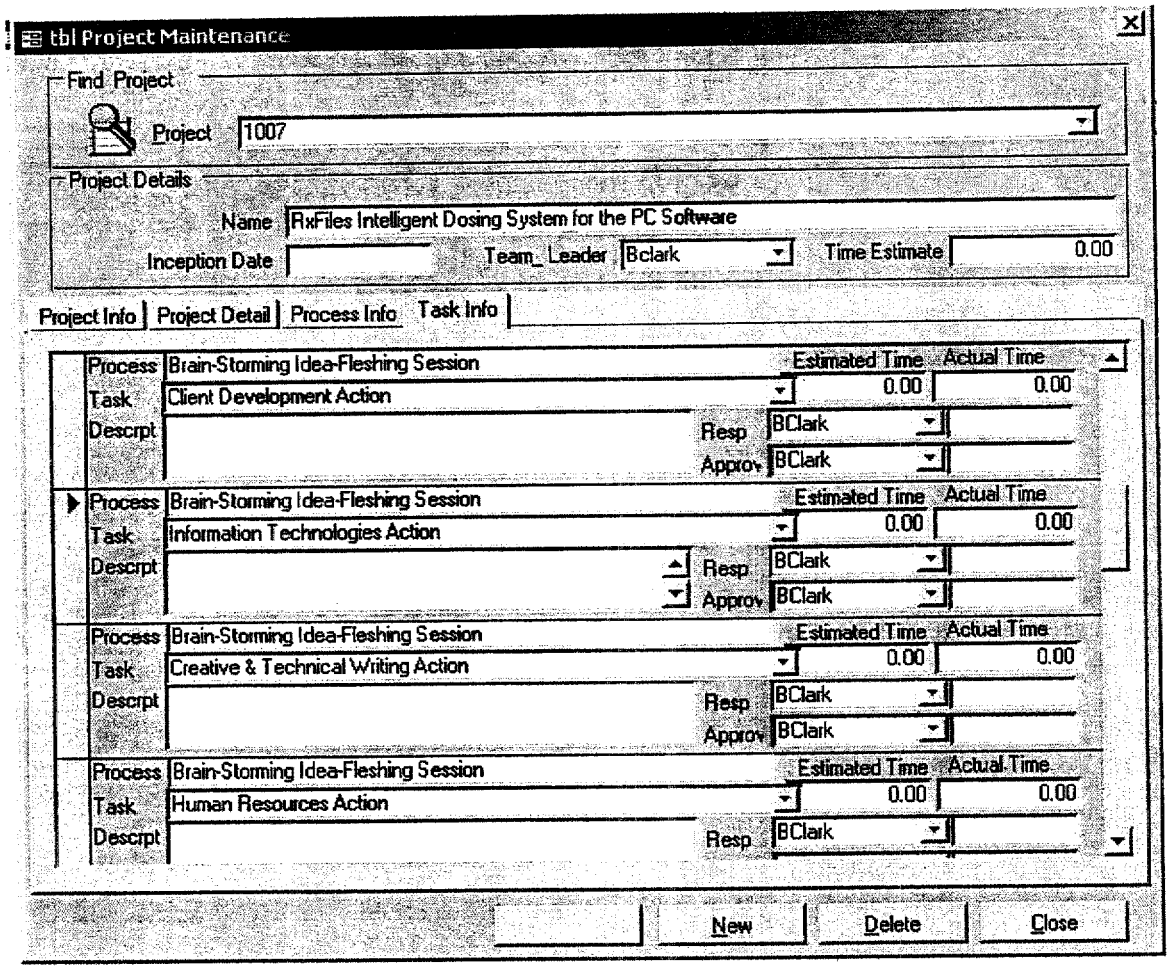
# **Overview**, Continued

The **Project Management System (PMS)** contains the Documented Project Detail, Process and Task Information registered and approved for internal release by The RxFiles Corporation, which includes, but is not limited to, testing results for verification and validation of each project version of the Intelligent Dosing System™ (IDS™) Agent Doser Calculators from all Departmental Functionaries.

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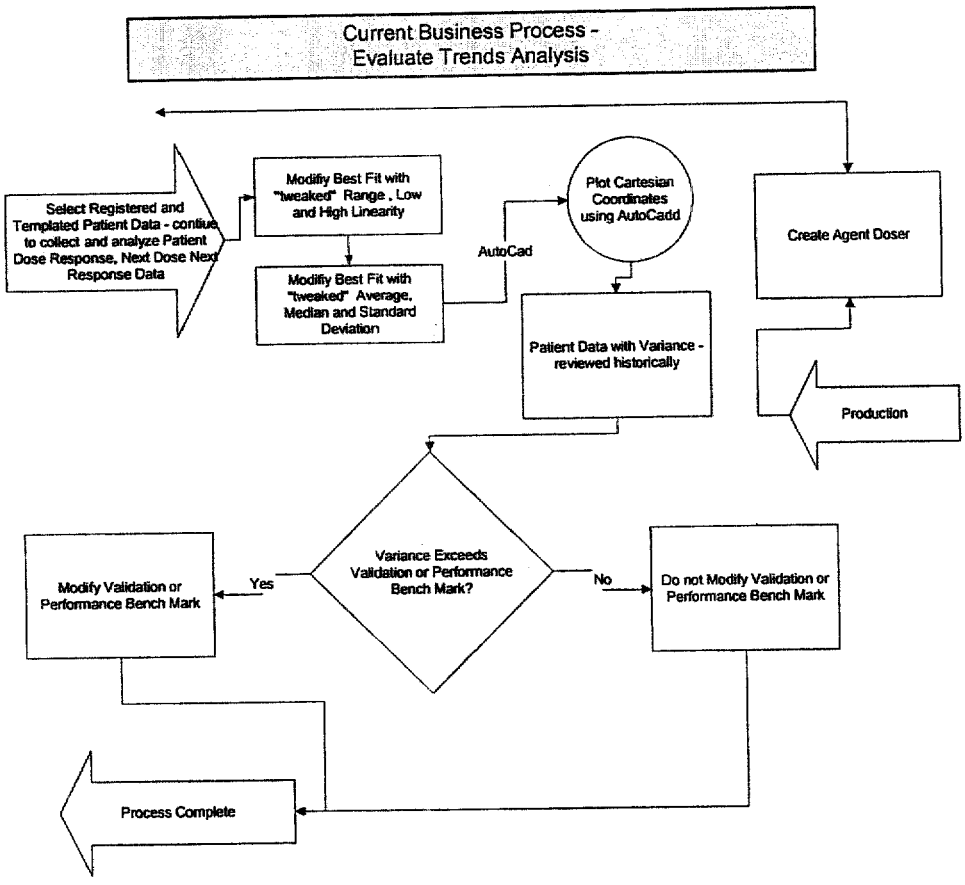
# Activity Requirements - Evaluate Trends Analysis

**Overview**

The Evaluate Trends Analysis process allows the Information Services Interface Personnel the ability to review periodically Agent Doser Requests and the incident Patient Data produced therefore. This protocal, which is part of the overall Quality Assurance Process, provides a historical, accumulative perspective regarding all data used to produce validity and bench mark items for present and future Agent Dosers. The current business process is very procedural and user intensive. Most of the actions required by the user are to be automated. This activity is considered to be a Key Performance Indicator of this project. See also: Evaluate Work-In-Progress/Work-in-route.

**Current Business Process - Evaluate Trends Analysis**

The current business process for Evaluate Trends Analysis is shown below.

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# Activity Requirements - Reconcile Best Fit with Patient Data, Continued

**Entity/ Relationships - Reconcile Best Fit with Patient Data**

The relationships in the entity relationship diagram (see appendix) are explained below. Please note these dependencies apply only to these entities in the context of Reconcile Best Fit with Patient Data.

Best Fit with Patient Data is a way of representationally modeling the various elements of the dose response, next dose next response curve incident to a Doser Agent Item produced during the Production of an Agent Doser. It was once necessary to compare various arbitrary selections of low and high degree of linearity for a given Agent in order to reconcile a Best Fit with Patient Data. Our quality assurance program has eliminated the necessity for the inclusion of these elements.

Over the course of providing dose response, next dose next response relationships for our initial Agent Dosers we recognized the fact that we could substitute the numeral one (1) for the Degree of NonLinearity at the Low end or for the Degree of NonLinearity at the High end. All that is necessary to perform a best-fit analysis are the Cartesian coordinates along the customary increments of the known range from zero (0) to the Maximum Dose for that Agent. Any variance that exceeds the customary validation or performance benchmark is used to modify the performance benchmark. Otherwise the benchmark is retained as is. A crosscheck of the registered Best Fit with Patient Data is performed by Information Systems Interfacing Personnel and should reveal any anomalous situations. However, the following observations still apply, to-wit:

1. Typically an increase in dose will result in an increase in therapeutic efficacy.
2. Typically a decrease in dose will result in a decrease in toxicity.
3. The degree of increase in level is somewhat dependant on the degree of increase in dose.
4. Other factors, external to the dose-response curve relationship, act on the subject to also alter the dose/marker relationship.
5. When dosing a patient, the subject can only experience sub-therapeutic response, optimal therapy, or toxicity (although optimal therapy may involve subjecting the patient to some toxicity.
6. When external forces (other than the dose/response curve) act upon a subject, adjustments need to be made for them.

# SECTION 9
# RISK MANAGEMENT ACTIVITIES DURING THE SOFTWARE LIFE CYCLE

# SECTION 9: RISK MANAGEMENT ACTIVITIES DURING THE SOFTWARE LIFE CYCLE

# EXHIBIT 9.1
# SOFTWARE DEVELOPMENT LIFE CYCLE
# SUMMARY

(b) (4)

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# EXHIBIT 9.2
# LIFE CYCLE MODELS AND METHODOLOGIES

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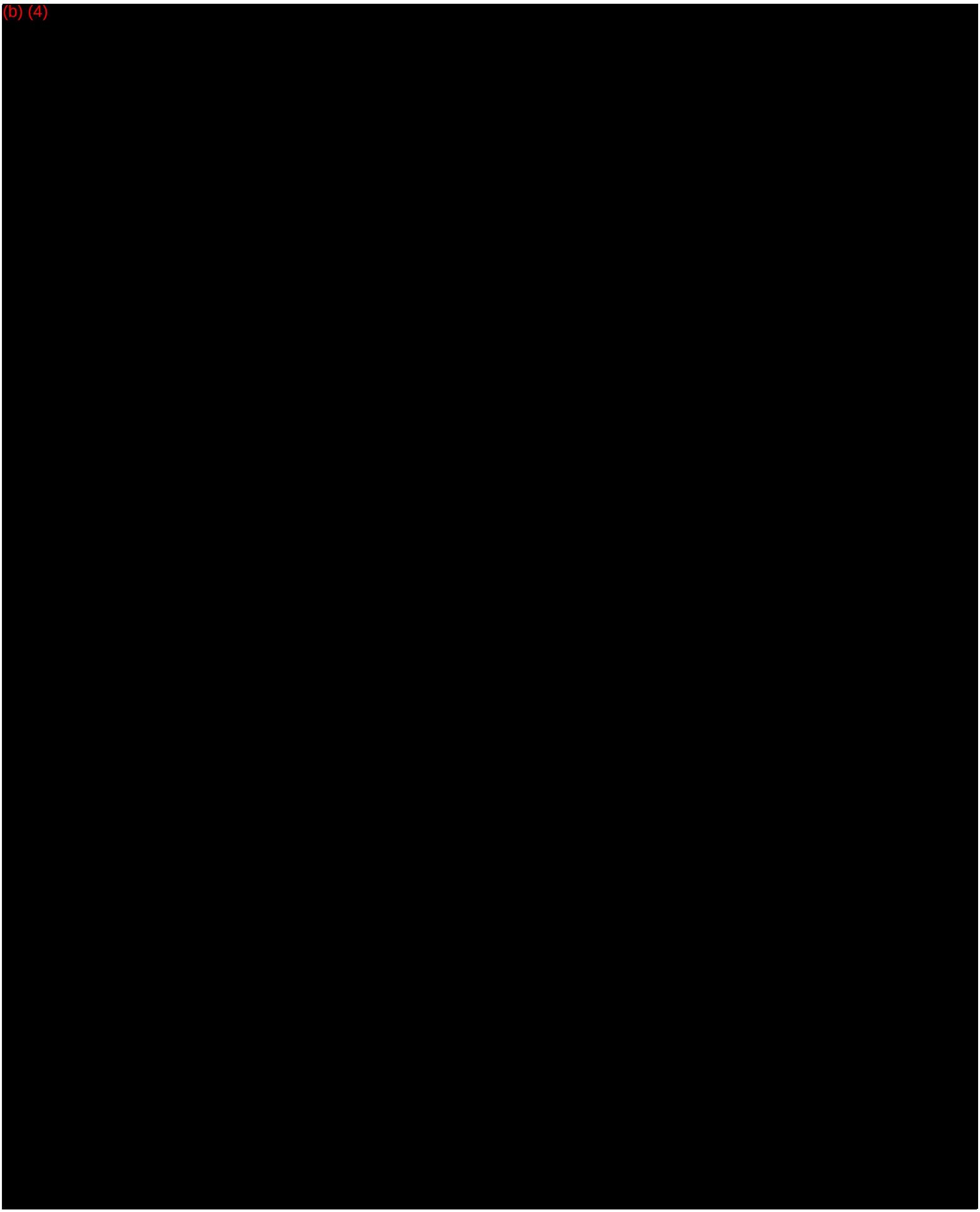

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(b) (4)

[redacted]

# EXHIBIT 9.3
# REQUIREMENTS ANALYSIS AND SPECIFICATIONS

(b) (4)

[redacted]

(b) (4)

[redacted]

# EXHIBIT 9.4
# RISK MANAGEMENT

## 4.3 Risk Management

4.3.1
4.3.2
4.3.3

See Documentation of all of our Tests at:

(b) (4)

[redacted]

# Activity Requirements - Evaluate Special Needs and Quantities

**Overview**

This process consists of evaluating the risks or hazards associated with of the use of the IDS™ Agent Doser. These are categorized into two groups; Internal and External. **Internal** hazards are those directly attributable to the nature of the designer formulae or the underlying calculator functionality. **External** hazards are those attributable to the user interface of the IDS™. Methods for assessing risk, mitigating, and minimizing or outright rectification of these are addressed in the Evaluate Special Needs and Quantities and the Normalize Data for Deseasonalized Demand sections of this document. There are five iterations of clinical evaluation regarding Internal hazards utilized in Agent Doser Production. Other review types are addressed in the Exception Processing section of this document. The Internal hazards review consists of Clinical and Engineering evaluations.

The **Clinical Evaluation** check list process includes both general operational and agent specific tasks to include both whole number (large = > 5digits) and decimal (to thousandths place) queries; repetitive data entry assessment, whole number entry assessment, decimal number entry assessment, increase marker/dose exercises, decrease marker/dose exercises and maintenance marker/dose exercises. Agent specific markers of toxicity and efficacy are acquired from the current Physicians Desk Reference and Merck manual and utilized for the above noted exercises. Dosing limits are evaluated as never less than one-half of previous dose and never more than twice previous dose. Subjective assessment markers and doses are utilized on the non-parametric section. The therapeutic interchanger is explored in the same manner with an equivalent brand, generic (if available) and differing class (but same marker effect) of agent utilized. The practice prescriber is evaluated by entry of high, low and best effort accuracy data.

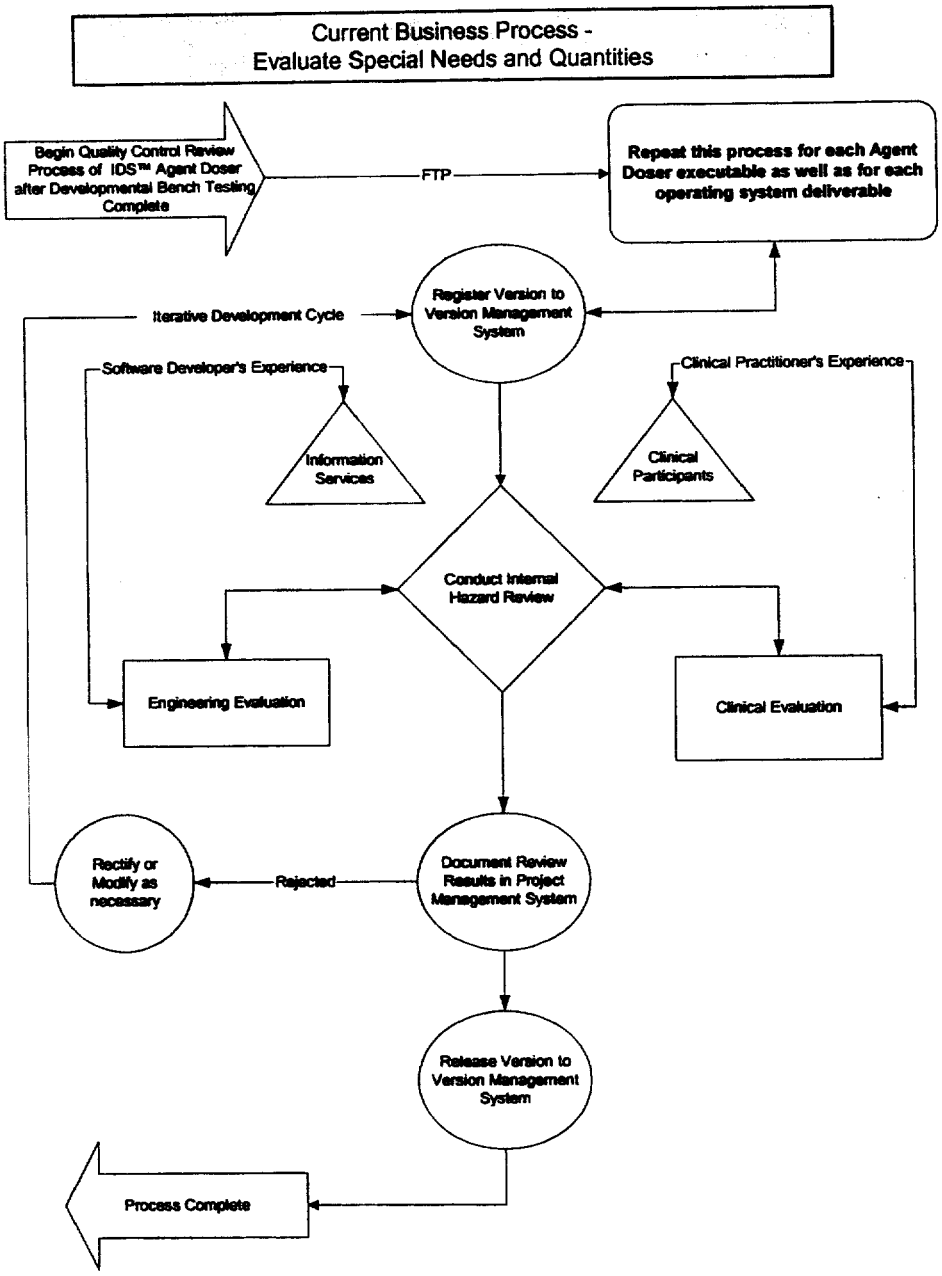
The **Engineering Evaluation** check list includes both performing static and dynamic functionality load tests, as well as checking for operating system specific anomalies, together with appraisal of software incidental and operational "bugs". From reviewing correct ignition and sequencing of the chronologically based application features, to checking the installation setup routines for proper functioning, as well as, investigations of timing and accuracy with regard to user interfaces, control switching and focus, including on focus and lost focus event handling strategies are critically analyzed for technically excellent operation. With specific regard to the IDS™ application software versions for use with personal digital assistants, palm and hand held devices, an inspection of the delivery, setup and operational procedures, as well as, typically required user interface protocols is conducted for thoroughness and ease of operation (the finite degree "user friendliness" is assessed). Each assessment so itemized, is registered and properly logged into the Project Management System, Quality Control section, by qualified Information Services Personnel.

*continued on next page*

# Activity Requirements - Evaluate Special Needs and Quantities, Continued

**Current business process - Evaluate Special Needs and Quantities**

The current process for Evaluate Special Needs and Quantities is shown below.

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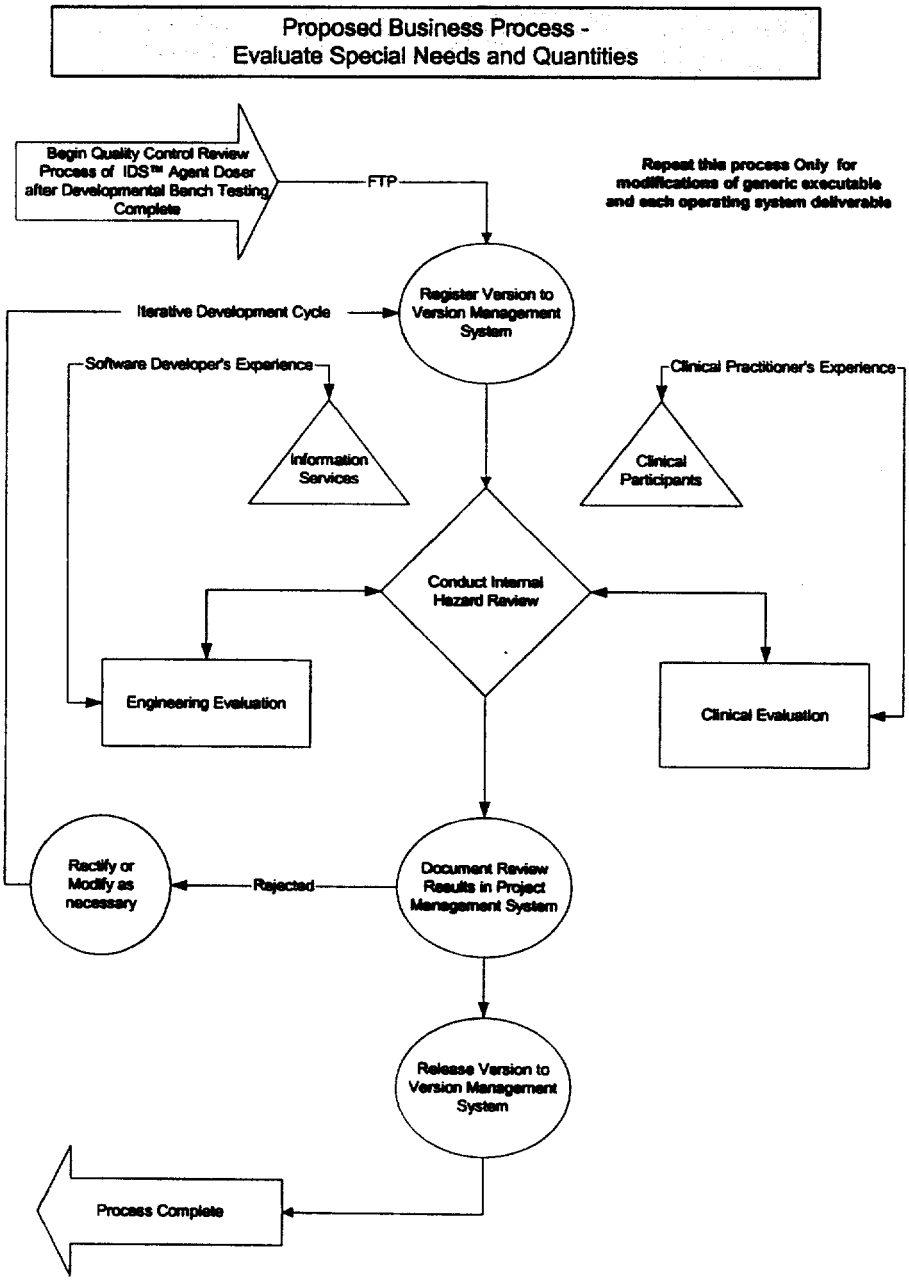
# Activity Requirements - Evaluate Special Needs and Quantities, Continued

**Proposed business process - Evaluate Special Needs and Quantities**

The proposed process for Evaluate Special Needs and Quantities is shown below.

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# Activity Requirements - Evaluate Special Needs and Quantities, Continued

**Information requirements - Evaluate Special Needs and Quantities**

The Evaluate Special Needs and Quantities process will **manage** the following information:

| Information | Description |
|---|---|
| Data Repository Review | A group of Data Repository Review Items to be conveyed to a Data repository for any given Agent. This review may "include" two or more Hazards. |
| Data Repository Review Item | A Doser Agent Item of a given range to be registered with a Data Repository for a Data Repository Review. (i.e. Weekly or Daily) |
| Engineering Evaluation | A group of Hazard Reviews performed by IT Professionals for all or part of a Data Repository Review Item for engineering hazards. |
| Clinical Evaluation | A group of Hazard Reviews performed by Health Care Professionals for all or part of a Data Repository Review Item for clinical hazards. |
| Internal Hazard Review | A review of processing functionality (all or part) of a Data Repository Review Item selected for Hazard Review. |
| External Hazard Review | A review of user interface protocols (all or part) of a Data Repository Review Item selected for Hazard Review. |

The Evaluate Special Needs and Quantities process will **access** the following information:

| Information | Description |
|---|---|
| Data Repository | The RxFiles Corporation Network facility to which product is placed for exposure to the Web Interface. This is usually a The RxFiles Corporation database. |
| Doser Agent Item | A Pharmaceutical Agent which has been reviewed and approved for inclusion in the VMS as a selectable Agent or as a member of an Agent Suite, and thereby exposed to the Web Interface. |
| Doser User | Any healthcare professional that has been supplied the IDS™ and encrypted parameters file from the Web Interface or other media. |

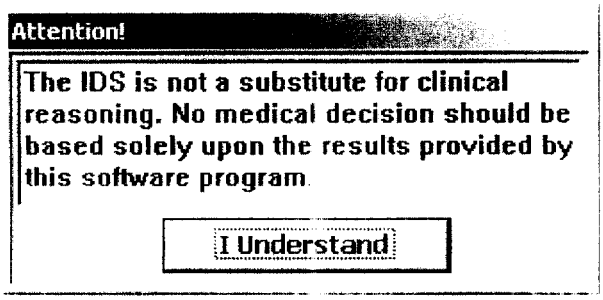
*continued on next page*

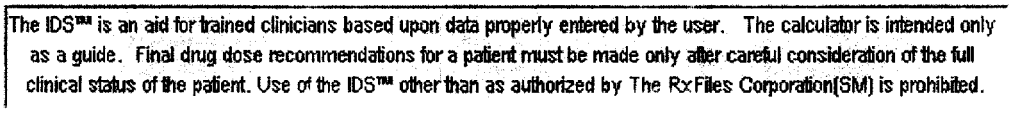
# EXHIBIT 9.5
# DOCUMENTATION

4.3 Documentation

There are no real hazards in running our software. It is an equation. The user may enter incorrect data/parameters, but it is required that clinical judgment be used in final dosing decisions. Ultimately, doses will be assigned not by our device, but by the professional prescriber.

These are the warnings found in our software



# SECTION 10
# VALIDATION VERIFICATION TESTING

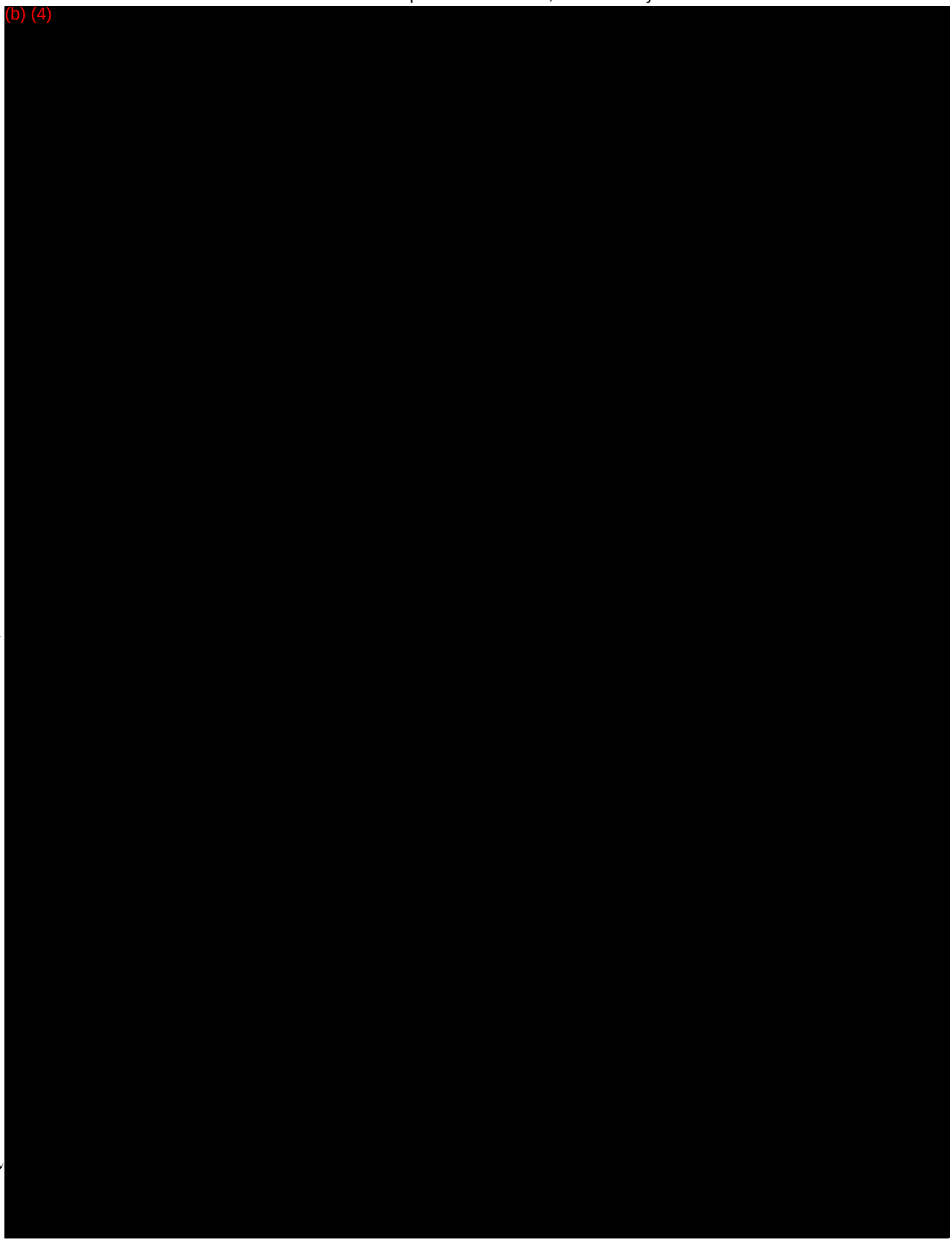
# SECTION 10: VALIDATION, VERIFICATION AND TESTING

**10.1 Verification and Validation Testing**
Reference Exhibit 10.1

**10.2 Unresolved Anomalies (Bugs)**
There are no bugs in the software

# EXHIBIT 10.1
# VERIFICATION AND VALIDATION

(b) (4)



3.9 For Validation, Verification, and Testing. See all of our Tests at:

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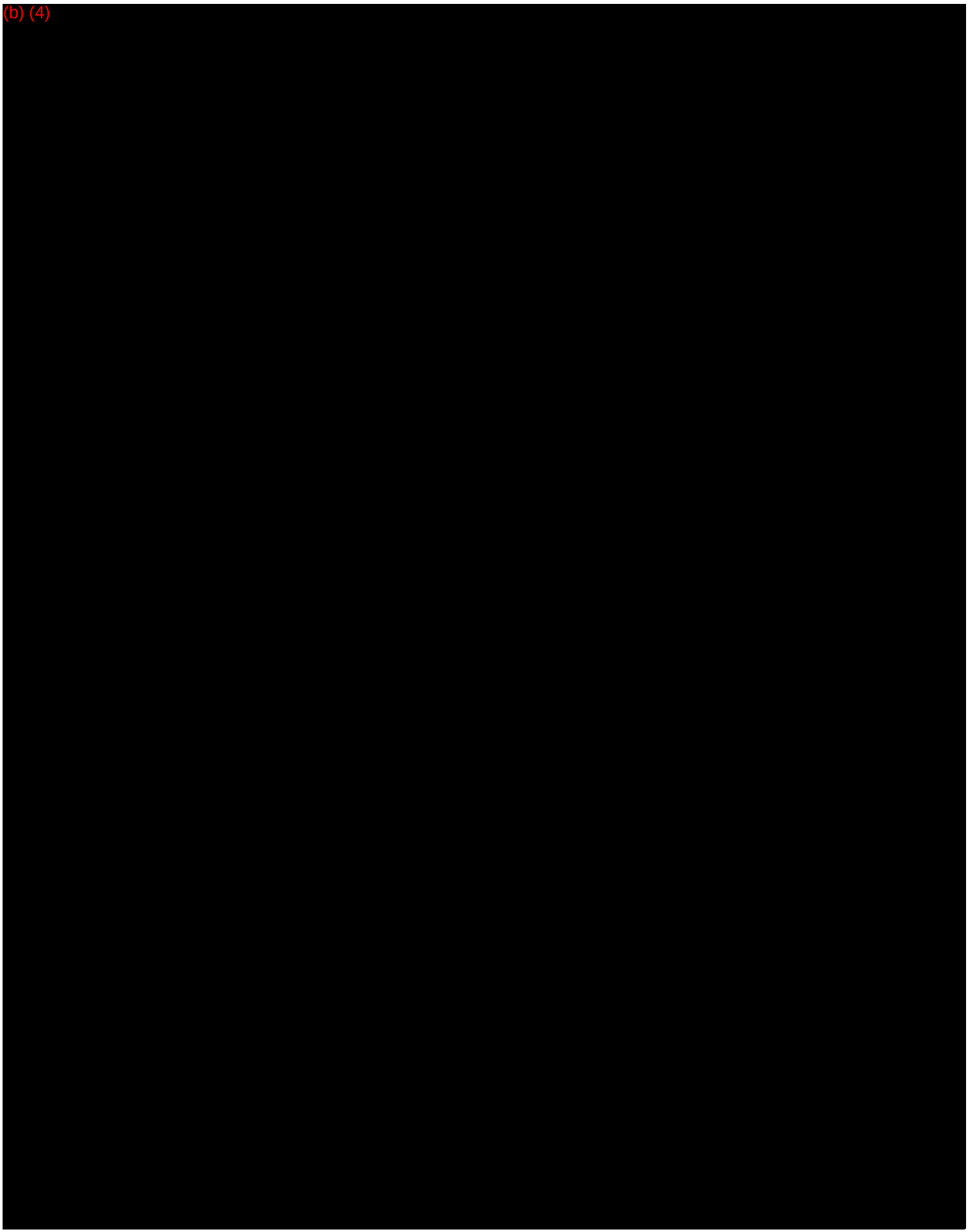

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# SECTION 11
# PREDICATE PRODUCT COMPARISON

# SECTION 11: PREDICATE PRODUCT COMPARISON

## 11.1 Intended Use:

The Intelligent Dosing System (IDS)™ is a three-part software suite comprised of DoseRx™, InterchangeRx™ and PracticePrescribeRx™. The DoseRx™ is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRx™ is designed to switch a patient from one brand of agent to another while maintaining the therapeutic effect of the original agent. The PracticePrescirbeRx is a dosing simulator that offers graded prescriber training of next dose calculation scenarios with scalable patient response and surrogate marker inputs that allows the healthcare provider to gain guided and measured experience in calculating the next dose for a new or infrequently used drug.

The IDS™ is not a substitute for clinical reasoning. The IDS™ is an aid for trained clinicians based upon significant and properly entered data. Final drug dose recommendations for a patient must be made only after careful consideration of the full clinical status of the patient. No medical decision should be based solely upon the results provided by this software program.

## 11.2 Substantial Equivalence Comparison Table:

| | IDS™ Dosing System | PDT DoseCalculator |
|---|---|---|
| **K Number** | | K000418 |
| **Intended Use:** | DoseRx™ is designed to calculate any individual patient's optimal next dose for any given agent. Interchange Rx is designed to switch patient from brand to another, maintaining therapeutic effect of original agent | To assist in the calculation of photodynamic therapy drug Dose based on inputs of height weight, mass etc. depending on the drug manufacturer's directions for use. |
| **Device Description:** | IDS™ is a three part software Suite comprised of DoseRx™, a "next" dose calculator, InterchangeRx, a therapeutic Interchanger to switch a patient from one agent, brand or class of drug to another, and Practice Prescribe Rx™, a graded prescriber stimulator. All IDS™ software can be accessed with Palm Pilot®, Windows, or Windows CE® Operating Systems. | The RetinaLabs.com, Inc PDT DoseCalculator is a simple personal computer software program that calculates the drug dose based on inputs of height, weight, mass etc. Replaces an archaic, inefficient and error-prone manual graphical nomogram technique. |
| **Software Based** | yes | yes |
| **Dose Calculation:** | yes | yes |

**Sterility:** The device is not required to be sterile

## 11.3 RetinaLabs.com PDT Dose Calculator FDA Letter and Summary: Reference Exhibit 11.1

# EXHIBIT 11.1
# PREDICATE PRODUCT INFORMATION

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Frank Tighe
President
RetinaLabs.com
1776 Peachtree Street
200 North
Atlanta, Georgia 30309

OCT 2 4 2000

Re: K000418
Trade Name: PDT DoseCalculator
Regulatory Class: II
Product Code: NDC
Dated: August 8, 2000
Received: August 10, 2000

Dear Mr. Tighe:

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 (for the indications for use stated in the enclosure) to 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). 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.

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. A substantially equivalent determination assumes compliance with the current Good Manufacturing Practice requirement, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic (QS) inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, 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 sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4595. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

for Celia M. Witten, Ph.D., M.D.
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

K000418

RETINALABS.com

K000418

**510(k) Number:** N/A

**Device Name:** PDT DoseCalculator (Personal Computer Software)

**Indications for Use:** To assist in the calculation of photodynamic therapy drug dose and treatment based on patient body surface area, weight, or mass depending on the drug manufacturer's directions for use.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ___X___ (Per 21 CFR 801.109) OR Over-The-Counter Use _____

(Optional Format 1-2-96)

(Division Sign-Off)
Division of General Restorative Devices
510(k) Number K000418

OPI

1776 Peachtree Street • Suite 200 North • Atlanta, Georgia 30309
Toll-Free (800) 793-1473 • Direct (404) 443-2831 • Fax (404) 873-3582 • Internet www.RetinaLabs.com





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301

**Device Description:** The RetinaLabs.com, Inc. PDT DoseCalculator is a simple personal computer software program that calculates the drug dose based on inputs of height, weight, mass etc. Replaces an archaic, inefficient, and error-prone manual graphical nomogram technique. Please see Device Replica Diagram in Appendix C.

**Statement of indications for use.** - To assist in the calculation of photodynamic therapy drug dose and treatment based on patient body surface area, weight, or mass depending on the drug manufacturer's directions for use.

## Substantial Equivalence Comparison

| | Body Surface Area (BSA) Calculator Hemotech Inc. | Dose Calculator Integrity Medical Software | PDT DoseCalculator RetinaLabs.com |
|---|---|---|---|
| Software Based | X | X | X |
| BSA Calculation | X | | X |
| Dose Calculation | | X | X |

## Sterility

The Device is not required to be sterile.

Return to Search

| | |
|---|---|
| **Device Classification Name** | CALCULATOR, DRUG DOSE |
| **Regulation Number** | 868.1890 |
| **510(k) Number** | K000418 |
| **Device Name** | PDT DOSECALCULATOR, MODEL 80000 |
| **Applicant** | RETINALABS.COM<br>1776 PEACHTREE STREET<br>200 NORTH<br>ATLANTA,GA30309 |
| **Contact** | FRANK TIGHE |
| **Product Code** | NDC |
| **Date Received** | 02/08/2000 |
| **Decision Date** | 10/24/2000 |
| **Decision** | SUBSTANTIALLY EQUIVALENT |
| **Classification Advisory Committee** | General & Plastic Surgery |
| **Review Advisory Committee** | General & Plastic Surgery |
| **Statement/Summary/Purged Status** | Summary only |
| **SUMMARY/Approval Letter** | SUMMARY |
| **Type** | Traditional |
| **Reviewed by Third Party** | No |

*(Database Updated May 7, 2001)*

OCT 24 2000

K000418

February 4, 2000

## Premarket Notification [510(k)] Summary

**Submitter:**
RetinaLabs.com, Inc.,
1776 Peachtree Street Suite 200 North
Atlanta, GA 30309

Phone: (404) 815-5233
Fax: (404) 873-3582

**Official Correspondent:** Frank J. Tighe

**Trade Name:** The RetinaLabs.com, Inc., PDT DoseCalculator

**Common Name:** Personal Computer Software

**Registration Number:** 1063514

**Class:** Class 1

**Class Name:** We were unable to find the device listed in the classification regulations, 21 CFR Parts 862-892 [807.87 (c)].

**Panel:** Ophthalmic

**Product Code:** N/A

# FDA/CDRH IMAGING SYSTEM

## Page Count Discrepancy Information

Page #6 was moved behind page #103 for document order.

The page after page 124 was numbered 126.

4 pages after the page marked 294 were not numbered.

Verifiers Initials