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Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service



AUG - 9 2001

Food and Drug Administration 9200 Corporate Boulevard Rockville MD 20850

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 <u>Code of Federal Regulations</u>, 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 <u>Federal Register</u>. 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.

Page 2 - Ms. Yolanda Smith

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 <u>in vitro</u> 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,

Mark A Millierse

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 $(IDS)^{TM}$ is a three-part software suite comprised of DoseRxTM, InterchangeRxTM and PracticePrescribeRxTM. The DoseRxTM is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRxTM 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					
	(Division Sign-Off)				
	Division of General, Restorative				
	and Neurological Devices				
Questions? Contact F	DA/CDRH/OCE/DID at CDRH-FOISTATUS@tda.phsgov or 301-796-8118				
FOI - Page 5 of 437	510(k) Number $(0.00000000000000000000000000000000000$				

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service Food and Drug Administration

ite:	8/13/DI
om:	DMC (HFZ-401)
bjec	t: Premarket Notification Number(s): KULS7/JA
	Division Director: SUI dama
•	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. <u>w</u> <u>r</u> 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: 344 OK. 19/12/0
	Date:

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



~ 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.

ganda Smith Sincerely,



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 8 of 437

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~ FDA CONSULTANTS ~

Specializing in Regulatory Affairs

August 9, 2001

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 22 of 437



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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 29 of 437 \mathcal{U}

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Public Health Service



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Page 2 - Ms. Yolanda Smith

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Sincerely yours.

Celia V. Witten, Ph.D., M.D.

Division of General, Restorative and Neurological Devices Office of Device Evaluation Center for Devices and Radio ogleal Health

Enclosure

510(k) Number (if known): K011571

Device Name: TRxF Intelligent Dosing System^{1M}

Classification Panel: 868.1890

Indications for Use:

The Intelligent Dosing System (IDS)TM is a three-part software suite comprised of DoseRxTM, InterchangeRxTM and PracticePrescribeRxTM. The DoseRxTM is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRxTM 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.

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<u>(PLEASE DO NOT WRITE</u> Concurre	BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED) ence of CDRH, Office of Device Evaluation (ODE)				
Prescription UseA. or					
	⁰ (Division Sign-Off)				
	Division of General Restorative				
	and Neurological Devices				
Questions? Contact FDA/CDR	H/OCE/DID at CDRH-FOISTATUS@fdaphs.gov or 301-796-8118				
FOI - Page 33 of 437	510(k) Number $N \cup 1 > 1 = 0$				

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015 DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

From.	Reviewer(s) - Name(s) DELLAHAMMOND	Memorandum
Cubicot	K 0/1571	
Subject.	510(K) Number	
To:	The Record - It is my recommendation that the subject 510(k) Notification.	
Is Is V I V S	Refused to accept. Requires additional information (other than refuse to accept). Image: Stantially equivalent to marketed devices. Image: Dother substantially equivalent to marketed devices. De Novo Classification Candidate? Image: Other (e.g., exempt by regulation, not a device, duplicate, etc.) St this device subject to Postmarket Surveillance? St this device subject to the Tracking Regulation? Vas clinical data necessary to support the review of this 510(k)? St this 510(k) reviewed by a Third Party? Special 510(k)? Abbreviated 510(k)? Please fill out form on H Drive 510k/boilers	□ NO S I 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 an Material of Biological Origin YES	d after)
I No o	The submitter requests under 21 CFR 807.95 (doesn't apply for SEs): Confidentiality	y exceeding 90 day
	Predicate Product Code with class: Additional Product Code(s) with p	anel (optional):
Revised:	NDC, I, 868.1890 Review: Arthrophic GSDB 8/3 (Branch Chief) (Branch Chief) (Date (Division Director) (Date 8/17//99 (1)	$\frac{1}{2}$

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FOI - Page 34 of 437

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015



Screening Che	cklis	t					
For all Premarket Notification	510	(k)	Subr	nissi	ions		3-30-01
Device Name: TRFX DOSING SYSTEM (105)						K 011	571
Onthe (Company): THE RX FILES COMPAN	NY						
Submitter (Company).			A		ĩ	.	
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Items which should be included	ا ۵		A		C) i	
(circle missing & needed information)	Ĺ		T		N L		✓ IF ITEM
	1		0		í	<u> </u>	NEEDED
	YES	NO	YES	NO	YES	NO	AND IS
1 Cover Letter clearly identifies Submission as:							MISSING
a) "Special 510(k): Device Modification"			-				
b) "Abbreviated 510(k)"		41.40			Y		
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) SU	IBMIS	SIONS	6				NEEDED
Financial Certification or Disclosure Statement for 510(k)s with a		NA	YE	S	N	0	
Clinical Study 807.87(i) including forms 3454 and/or 3455			10000	TATED	TRADI	TIONAL	
	SPEC	NO	VES	NATED	YES	NO	MISSING
the time and establishment registration	120		120				
a) trade name, classification name, establishment registration							
b) OB a statement that the device is not yet classified	FDA-r	nay be	a classi	fication	reques	st; see c	oordinator
c) identification of legally marketed equivalent device	N	A			V		
d) compliance with Section 514 - performance standards	N	A			V		
e) address of manufacturer					V		
f) Truthful and Accurate Statement					V		
g) Indications for Use enclosure					~		
h) SMDA Summary or Statement (FOR ALL DEVICE CLASSES)					V		
i) Class III Certification & Summary (FOR ALL CLASS III DEVICES)							
i) Description of device (or modification) including diagrams,							
engineering drawings, photographs, service manuals	.	i i i					
k) Proposed Labeling:	ļ						
i) package labeling (user info)				+	- <u>×</u>	ALC: NO	
ii) statement of intended use							
III) advertisements or promotional materials	+	- 83			•	1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 - 1995 -	
MIRI comparison Information (similarities and differences) to named							
legally marketed equivalent device (table preferred) should include:							
i) Labeling							
ii) intended use							
iii) physical characteristics					\uparrow		
(v) anatomical sites of use	N	IA			·		
vi) safety characteristics	N	IA			•		1
m) If kit, kit certification					•		
3. "SPECIALS" - ONLY FOR MODIFICATIONS TO MANUFACTURER'S	OWN C	LASS I	, III OR	RESER	VED C	LASSI	
a) Name & 510(k) number of legally marketed	1						
(unmodified) predicate device							
b) STATEMENT - INTENDED USE AND INDICATIONS FOR			* If no	- STOP n	ot a spe	cial	
USE OF MODIFIED DEVICE AS DESCRIBED IN ITS		. gian i					

-Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs-gpv or 301-796-8118

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

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 Cont	rols)	
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		
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: Maintainer . Date: 7.25-01 Concurrence by Review Branch: 70
Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

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

011571 K

Reviewer: DELLA HAMMOND

Division/Branch: DGRD/G508

Device Name: TRXF INTELLIGENT DOSING SYSTEM (105)

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)?	V		If NO = Stop
3.	Same Indication Statement?	1		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 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:

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

Internal Administrative Form

┣			NO
		YES	NO
1.	Did the firm request expedited review?		4
2.	Did we grant expedited review?		
3.	Have you verified that the Document is labeled Class III for GMP		r
	purposes?		1/
4.	If, not, has POS been notified?		-
5.	Is the product a device?	-	
6.	Is the device exempt from 510(k) by regulation or policy?		Ł
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?		
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		L
	investigation?		L
1	1. If, yes, consult the ODE Integrity Officer.	1997 - 1997 -	1
1:	2. Has the ODE Integrity Officer given permission to proceed with the		
	review? (Blue Book Memo #l91-2 and Federal Register 90N0332,		
	September 10, 1991.		l

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

FOI - Page 39 of 437

FROM : SMITH ASSOCIATES

Records Processed under FOIA Request # 2015-8339; Released by CDRH-0hl 113320001 12:08PM P1

Smith Associates

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

FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015



Questions? Contact FDA/CDRH/OCE/DID at CPRH FØISTATUS@fda.hhs.gov or 301-796-8118

FOI - Page 95 of 437

FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Jul. 23 2001 12:12PM P7 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

Software Validation & Verification (b) (4)

Questions? Contact FDA/CDRH/OCE/DD at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 96 of 437

FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

Software Validation & Verification (b) (4)

Questions? Contact FDA/CDRH/OCE/DHD at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 97 of 437 FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Jul. 23 2001 12:11PM P5 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

Software Validation & Verification (b) (4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 98 of 437 Software Validation & Verification (b) (4)

Questions? Contact FDA/CDRH/OCE/DID at CØRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 99 of 437 FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Jul. 23 2001 12:09PM P3 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

Software Validation & Verification (b) (4)

FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015 12:09PM P2



Questions? Contact FDA/CDRH/OCE/DID at CDRH, FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 101 of 437 FROM : SMITH ASSOCIATES FAX NO. : Records Processed under FOIA Request # 2015-8339; Released by CDRH of 11-9-2015 36AM P1 1/28/0/

Smith Associates

P.O., Box 4341 Crofton MD, 21114 Tel: (410)451-0639 Fax: (410)793-0448 E mail: <u>YSmith9746@aol.com</u> 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__

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Testing of PC applications: Software Validation & Verification (b) (4)

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Testing of Palm Applic Software Validation & Verification	(b) (4)	.1	

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Software Validation & Verification (b) (4)

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FROM : SMITH ASSOCIATES Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015 P-3 Jul 16 01 05:00 P

Software Validation & Verification (b) (4)

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System Context Diagram, Continued

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FOI - Page 108 of 437

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Activity Requirements - Evaluate Special Needs and Quantities, Continued

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FROM : SMITH ASSOCIATES FAX NO. : Jul. 20 2001 09:41AM P10 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015 P.9 Jul 19 01 05:06 P.

Activity Requirements - Evaluate Special Needs and Quantities, Continued

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Activity Requirements - Evaluate Special Needs and Quantities, Continued

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Activity Requirements - Evaluate Special Needs and Quantities, Continued

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FROM : SMITH ASSOCIATES FAX NO. : Jul. 20 2001 09:42AM P14 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

TRxF Clinical IDS Evaluation Procedure



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FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Jul. 23 2001 12:25PM P1 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

Smith Associates

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

FROM : SMITH ASSOCIATES PHONE NO. : 4107930448 Jul. 23 2001 12:28PM P7 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

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FROM : SMITH ASSOCIATES Records Processed under FOIA Request # 2015-8339, Released by CDRH on 17-9-2015 12:26PM P4



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Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015 DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

> 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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-7\$6-811

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Records Processed under FOIA Request # 2015-8339; Released by CORH of 9-9-2015/

RxFiles Intelligent Dosing System 510(k)

ANJ

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Records Processed under FOIA Request # 2015-8339; Released by CARH 0011-9-2915 71

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 Do	se		
Common/Usual Name:	Dose Calculator			
Proprietary Name:	TRxF Intelligent Do (IDS [™]) –Dosing Ca	osing Sy alculato	ystem™ r Suite	
Establishment Registration Number:				
Classification:	NDC		- - 	FOA
Classification Panel:	868.1890		<u>a</u> in a star	/808/
Labeling/Product Information/Promotional N	Material:		e Principal Maria and Maria and Maria and Maria and Maria	/300
Indications for Use, Product Description:	Reference Section 1	n an a Tangaté		0MC
Labeling: User Manual (Help Files) Website and Product Literature:	Reference Section 2			
Equation Formula:	Reference Section 3			
Hazard Analysis	Reference Section 4			2
Software Requirement Specifications:	Reference Section 5			F
Design Specifications:	Reference Section 6			

Questions? Contact FDA/CDRH/OCE/DP a CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 135 of 437

Software Traceability Matrix: R	
	<pre>{eference Section 8</pre>
Risk Management Activities: R	Reference Section 9
Comparison of Predicate Devices:RCompanyProductRetired abs comPDT DoseCalculator	Reference Appendix 10 <u>510(k)#</u> 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,

lal S. J

Yolahda 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.

JOHN D. KUT2KO (Typed Name)

<u>MAY 10, 2001</u> (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

(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)TM is a three-part software suite comprised of DoseRxTM, InterchangeRxTM and PracticePrescribeRxTM. The DoseRxTM is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRxTM 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

Questions? Contact FDA/CDRH/OCE/DID at CDRH4FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 139 of 437

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GLOSSARY OF TERMS

Aaverse 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.
Al 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 fluiv volumes."
BIA	Bioelectrical Impedance Analysis
BIS	Bioelectrical Impedance Spectroscopy
СРТ	Common Procedural Terminology (Codes are referenced from the American Medical Associations handbook, Comm 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 instrument
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 Phase 1 Clinical Trials Phase 2 Clinical Trials Phase 3 Clinical Trials Phase 4 Clinical Trials	Pre-clinical testing of several dosages over relevant time periods on at least two species Small doses on healthy volunteers: <u>pharmacokinetics</u> and side effects Small sample of hospital patients Broader clinical trials on patients
Distinguis	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.
Pretrivsmography PRACTICE PRESCRIBERx™	The gathering of physical data pertaining to organ, limb, fat and or hydration composition. (Patent Pending 7/14/00) "Software products to provide prescribing simulations." This is part of the IDS product offering.
controlled clinical trials(SM) Surrogate Marker	(SM Pending 7/14/00) "Unspecified medical related services."
TBW	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. 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.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

SECTION 1 INDICATIONS FOR USE, BACKGROUND, SOFTWARE DESCRIPTION

Questions? Contact FDA/CDRH/OCE/DID at ODRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 144 of 437

SECTION 1: INDICATIONS FOR USE, BACKGROUND, SOFTWARE DESCRIPTION

1.0 Intended Use:

The Intelligent Dosing System (IDS)TM is a three-part software suite comprised of DoseRxTM, InterchangeRxTM and PracticePrescribeRxTM. The DoseRxTM is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRxTM 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 principles 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 IDSTM is based on a precursor of Enhanced IntelligenceTM from an Expert Computer System featuring an artificially intelligent modeling systemTM (AIMSTM). The AIMSTM 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 DoseRxTM includes all available information about the subject drug as well as what steady and dynamic state dose is to <u>surrogate marker</u> (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 $DoseRx^{TM}$ 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^M 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^M method utilizes our Enhanced IntelligenceSM 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 InterchangeRxTM.

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 (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 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 RC³T'sTM, using the IDSTM 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 IDSTM provides the means to establish the most safe and effective dose through rapid titration in RC³TTM type testing. Because the IDSTM 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 IDSTM 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.

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

1.6 **Product Sample**

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

The Rafiles Corporation - Intelligent Do	and but the work of the second			en para sangganta	When you open the IDS
This doser is licensed t	o:	· · · · · · · · · · · · · · · · · · ·	Ar: 1.03122001094313		software program, the default screen is set for
Dr. John Q. Doe, MD,	PhD	Select An	Agent: Cyclosporine	-	the parametric DoseRx calculator.
DoseRx™	Interchange	Rx™	Practice Pres	cribeRx™	After you have selected your agent, point your
C	;yclosporin	e DoseRx™			cursor at, and click on, the Current Drug Dose
IDS [™] DoseRx [™] Parametric#	Objective	IDS 🍽 Dosefu	** Honperemetric/Sul	vjective	to type in the numbers
Poremetric Colculator					that correspond with the patient's most recent
Current Brug Dose: 750.00					dosee.
Current Marker: 350.00					Press the Enter key to
Besired Marker: 300.00		When you enter the Do and will fill in the New I	esired Marker, the calcul Jose, Suggested Dose, (ator is activated and Predicted	 continue to the next field and type in patient's
Previous Marker:		Marker. If the patient's	Previous Marker was N	Of the result of an	Current Marker.
New Dose: 678.57		possibly distort the inte	anded result of the patie	nt's Desred	
Suggested Unit Dose: 675.00	Recalculate	Marker. This is because adjust to the individual	e the calculator's equations is response by its own of	n is designed to a	
Predicted Marker 297.50	L Europertad Linit	previous response not	generated by the IDS m	ay cause the	
on Unit Dose:	Dose will always be	equation to adjust to v from its last calculation	An exception to this or	nexpected result cours when the	
Help Clear	dosest available	Current Marker and De	sired Marker differ by le	ss than 10%.	
License Expiles: [20/02/2001				. <u></u>	
TR The DS is an aid for trained clini	icians based upon data pr	operty entered by the user.	The calculator is intended	only	
1 X as a guide. Final drug dose rec	commendations for a patient	nt must be made only after	careful consideration of the i		
Carta a parts of the parter. One	of the tuber of the state of th		Contraction (See) is taking		
	anter But interests . Sat Analy		میں اور	2122001004212	
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Dr. John G. Doe,	, MD, FND	N	Select An Ager	st: Cyclosporine	<u>.</u>
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Dosekx	Interd	changeRx ¹	Pra	ctice Pres	cribeRx™
	Cuoloc	norino Do	collyTM	• • • • • • • • • • • • • • • • • • • •	
	Cyclus	puine Du	SCKY	· ····	
IDS ¹⁰ DoseRx ¹⁴ Paren	netric/Objective	1	OS TH DoseRx TH No	nparametric/Su	bjective
Parametric Calculator					
Current Brug Boese 7	50.00	Notice t	hat by entering a Pr	evious Marker tha	t had been
	0.00	guided i Desired	by the IDS in which t Marker of 300, the 1	he patient did not Suggested Dose d	acheive the ronned from
Booired Horkors	<u>0.00</u>	675 to (500, in order to adju	st to the patient's	over-response
	00.00	to the k	ast dose.		
Previous Marker: B					
New Dose: 59	10.87	, Now, be	cause the New Dose	would ideally be !	590.87
Suggested Unit Dose: 6()0.00 Recei c	ulate (an amo	unt Cy A is not avail	able in), the closes	st
Predicted Marker	6 20	Suggest	ed Dose is 600, which wite down to 300. If	h will still not take the user would li	the
on Unit Dose:	0.35	see wha	t Predicted Marker w	ould occur if a low	ver (
tielo Cie	ar	dose of	575 were manually e	ntered, point you Doce and state	r
	l	A Backspa	te over the Dose of	600, type in 575,	and
License Expires: 05/02/2001		Aclick on F	Recalculate.		
- 1					
TRE The IDS ^m is an aid for tra	ined clinicians based	upon data property enti	ned by the user. The	calculator is intended	only
I X I as a guide. Final drug	dose recommendation	ns for a palient must be	made only after careful	consideration of the	MI Close
1 clinical status of the pati	ent. Use of the IDS ^{ma}	other than as authorize	by The RxFiles Comp	pration(SM) is prohibi	ted.

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SECTION 2 LABELING

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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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

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 152 of 437

EXHIBIT 2.1 INSTRUCTION MANUAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

A Guide to Using The Intelligent Dosing System



The IDSTM 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



Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 20 FOI - Page 154 of 437

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Doc-To-Help

Contents • i

General Information

Selecting An Agent

To select an agent for any portion of the IDSTM software suite ($DoseRx^{TM}$. Interchange Rx^{TM} , or Practice Prescribe Rx^{TM}) 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 $DoseRx^{TM}$, Interchange Rx^{TM} , and Practice Prescribe Rx^{TM} the calculator's equation is set for that agent.

e RxFiles Corporation - Intelligent	Dosing System TH	a supervised of the supervised of the	10000		
This doser is licens Dr. John Q. Doe, N	ed to: D, PhD	Select A	In Agent: Dyclospotin		Ī
DoseRx™	Interchan	geRx™	Practice Pr	escribeRx	TM To select an agent, point your cursor at
	Cyclospor	ine DoseRx ^T	M		and scroll to the agent you want to dose.
IDS™ DoseRx™ Parame	tric,Objective	IDS™ Dose	Rx™ Nonparametric	/Subjective	When you have the correct agent in
Parametric Calculator			N N		highlight, single click
Current Drug Dose: Current Marker: Desired Marker: Previous Drug Dose: Previous Marker:					Or, dick your cursor in this field and using your keyboard type the name of the agent you want to dose, and
New Dose: Suggested Unit Dose:	Recalculate			ļ	press the enter key.
Predicted Marker on Unit Dose: Help: Print: Cle	ar Inverse Markers			When your ag appears here, to calculate no	ent's name you may proceed ext dose.
License Expires: 05/02/2001					

2 • General Information

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 IDSTM 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.

This doser is I Dr. John Q. De	icensed to: be, MD, PhD	When you open the IDS software, the default screen Select set for the parametric DoseR: calculator for objective
DoseRx™	Intercha	ngeRx TM surrogate markers.
	Cyclospo	rine DoseRx™
IDS [™] DoseRx [™] Pa	rametric/Objective	After you have selected an agent, point your
Parametric Calculator		Drug Dose, and using your keyboard type in the
Current Drug Dose: Current Marker: Desired Marker: Previous Drug Dose: Previous Marker:	750 350 300 	amount that represents the patients most recent dose. Using either the Enter or the Tab keys, continue on to the next field and enter the Current Marker, Enter/Tab again and enter the Desired Marker.
New Dose:	679 When you enter will fill in the Ner 675 Narker, so that patient's 2nd d	er the Desired Marker the calculator is activated and w Dose, the Suggested Unit Dose, and the Predicted t prescribers can make use of the ID5 with the ose.
Predicted Marker on Unit Dose:	298 If however the the prescriber those amounts	Previous Drug Dose and Previous Marker are available can realize a more accurate target dose by entering before continuing.

If your computer is connected with a compatable printer, point the cursor at the Print button and click on it to save a document for your patient's file, or to fax a copy to your pharmacy. To begin a new calculation for another patient, point your cursor at the Clear button and click.

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

This doser is licensed to: Dr. John Q. Doe, MD, PhD	Select An	
DoseRx™ Interchan g	eRx™	
Cyclospori	ne DoseRx™	
IDS™ DoseRx™ Parametric/Objective	IDS™ DoseRx	
Current Drug Dose: Current Marker: Desired Marker: Previous Drug Dose: Previous Marker: New Dose: Suggested Unit Dose: Predicted Marker on Unit Dose: Help Prints Clear.	To bose to reverse toxicity, and raise a vital parameter, point your cursor at this box and sing click. When check mark appears your agents calculator is recalibrated for inverse calculation.	
License Expires: 07/30/2001	property entered by the user.	

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 IDSTM DoseRx[™] Parametric/Objective box and click.

The RxFiles Corporation - Intelligent Do This doser is licensed Dr. John Q. Doe, MD,	sing System™ to: PhD		Ar: 1/16/2001 5:44:56 PM		To view the Nonparametric
DoseRx™ Interchan		IgeRx TM Practice Prescr		escribeRx™	the screen of the parametric calculator _by clicking on its Banner.
	Cyclospor	ine DoseRx™	l		
IDS™ DoseRx™ Parametric	/Objective	IDS" Dosel	Rx™ Nonparametric	/Subjective	
License Expires: 01/02/2001 T R F The DS Treases States the data relative	ship to gancing fields? a	Nonparametric Current Drug I Current Impress Response Desin Less Thera Therapeutic Resp Previous Impress Response Desin Less than Thera Expected Resp Less than Thera Expected Resp Less than Thera Expected Resp	Calculator Cose: ion of Response ed Response peutic More onse Therapeutic sion of Response peutic More than onse Expected Print Clear ions based upon data property se grandial condition. Final d	New Dose: Suggested Unit Dose:	Now dick on the Banner for the Nonparametric DoseRx, and this screer will appear.

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

The RxFiles Corporation - Intelligent Dosing System™		F 1. D-1-1-1-
This doser is licensed to: Dr. John Q. Doe, MD, PhD	Ver: 1/16/2001 5:44:58 PM Select An Agent: Cyclosporine	Inter Patient's most recent dose here.
DoseRx™ Practice PrescribeRx™ Practice PrescribeRx™		Using cursor and arrow, click on marker and slide it to percentage of percieved current
Cyclospo		
IDS™ DoseRx™ Parametric/Objective	IDS™ DoseRx™ Nonparametric/Subjective	response. Using cursor and arrow again, click and slide marker to percentage of previously percieved response. These fields will auto-fill with release of mouse click. Suggested Unit Dose will be closest available amount of agent being dosed.
License Expires: $01/02/2001$ T R F The DST ¹⁴ emonstates the core relationship to same an inter- mense. The calculator is instance way as a galaxy RF we make protestional. Use of the DST ¹⁴ there than by a qualified healthcare	Nonparametric Calculator Current Drug Dose: 650.00 New Dose: Current Impression of Response 546.73 Response Desired Response 546.73 Response Desired Response Suggested Less Therapeutic More Unit Dose: Therapeutic Response Therapeutic 550.00 Previous Impression of Response 550.00 State of Response 550.00 Previous Impression of Response Response 550.00 Previous Impression of Response Evented 8000000000000000000000000000000000000	

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.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
InterchangeRx[™] In Detail

The InterchangeRx^M 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^M.

View InterchangeRx[™] Calculator

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

The RxFiles Corporation - Intelligent Dosing System™			To view IRx from main	
This doser is licensed to:		Ver: 1/16/2001 5:46:10 PM		
Dr. John Q. Doe, MD. PhD	Choose Your Agent: Cyclosporine		InterchangeRx tab and Tclick once.	
DoseRx™ Intercha	ngeRx™	Practice PrescribeRx™	Enter last level and dose - of original agent (e.g.	
Cyclosporine	- Neorol), allowing this to be your new dose and			
Original Agent/Drug	Original Agent/Drug New Agent/Drug			
Initial Dose/Level	Subsequent Sur	regate Markers and Doses	After the first dama and	
Level: 350.00			reasonable time frame,	
Dose: 500.00	475.00		check patient level, and enter marker here. Press Enter or Tab key.	
Unit Dose:	475.00			
Ciéar	Observation 1 0	bservation 2 Observation 3	These fields will auto-fill with Unit Dose being the closest available dose amount for this agent.	
Print NOTE: When switching betwee	en brands and generics	, initially keep patient on same dose.	Remember to make note	
NOTE: This version of Interchar	ngeRx™ is not designe	d to change between classes of agents.	of the responses to enter them accurately for sequential Observations 2 & 3.	
			-	
$T \mid R_X \mid F$ The IDS-Wademonstrates the dose relativeship to surveyable matters the user. The calculator is intended only as a guide. It is not intend recommendations for a patient must be made only after careful interpr	as an aid for trained beamcare pr led to diagnose, treat of care any relation of the entire clinical status	réssionais based upon data properly entered by Esease of medical condition. Final drug dose of the patient by a qualified healthcare		

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.

10 • InterchangeRx[™] In Detail **Doc-To-Help** Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 \odot O

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.

This doser is licensed to: Dr. John Q. Doe; MD. P	hD ();); _	Ver: 1/16/2001 5:46:10	PM	
		Choose	Your Agent: Hearing	u: <u> </u>	
DoseRx [™]	nterchange	RxTN	Practice P	rescribeRx TM	
Tacrolin	nus Practic	ce Presc	ribeRx™		
ENTER THE DAILY	DOSE YOU WO	OULD PRESC	RIBE		peint your cursor to a Practice PrescribeRx I and single click.
Patient's curre	int dose is: 8.00	~~			
Patient's desired	Marker is: [3.22			A simulated p	atient history will auto
The last time the patient was dosed a	change of:	0.65 waa	expected in the Mar	ker. Cnce you beg	n to answer, the
I he actual change in the M	laiker was:	0.12		caculator will a your soare. الأسر	sulmaticaliy maintain
Help	piescibe?		Agreement;		
License Expires: 02/02/2001		Cu	mulative Average:		
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jfræssivaat. Use of the IDSPActher than by a ga	abled heathcare protessiona	land as interded by T	ie Bactiles Corporation is poulibried (

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

The RxFiles Corporation - Intelligent Dosing System™				
This doser is licensed to:	4025-33 37 3	Ver: 1/16/2001 5:46:10 P	M	
Dr. John Q. Doe, MD, PhD	Chr	oose Your Agent: Tacrolimu	s I	After you have reviewed the simulated patient
DoseRx™ Interchan	geRx™	Practice Pi	rescribeRx™	amount you would prescribe here, and
Tacrolimus Prac	tice Pre:	scribeRx™		press enter.
ENTER THE DAILY DOSE YOU	WOULD PR	ESCRIBE		
Patient's current dose is:	22.00		A diaid appea	gue dox will r on your screen
Patient's current Marker is:	8.41	/	with the dose.	ne correct next
Patient's desired Marker is:	1.14		Microsoft Acces	X
The last time the patient was dosed a change of:	-7.27	was expected in the Mar	ker. I would have pro	escribed 11.
The actual change in the Marker was:	-0.49		C OK	
How much would you prescribe?	11.00		<u></u>	
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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

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patient control loop to meter the dose in response to a surrogate marker which

may be objective, subjective, positive or negative.

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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 IDSTM 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?

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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

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Frequently Asked Questions • 13

Q. How does the IDS[™] individualize patient therapy?

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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?

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therapy. The

 IDS^{TM} simply provides a standardized "map" for the individual's expected dose to level relationship.

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relationship when modern PK-PD technology cannot?

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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^M Matrix is predictive rather than descriptive. With this in mind, the IDS^M is better suited for patient dosing.

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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^{TM} Matrix?

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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 Antidepressants 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 IDSTM?

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

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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.

Questions? Contact FDA/CDRH/OCE/DID at CDRH

FATUS@fda.hhs.gov or 301-796-8118

Support Information

Registration:

The Intelligent Dosing System's^M product support services are for registered users only; make sure that your software is registered with The RxFiles CorporationSM.

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 IDSTM 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.

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Doc-To-Help

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EXHIBIT 2.2 THE RXFILES CORPORATION WEBSITE

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Overview IDS Info BCA Info Purchase Reimbursement Dovinload Demo

Intelligent Dosing SystemTM (IDS)TM

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 Pilote, Windowse, or Window CEe Operating Systems. Additionally, use of our programs may be submitted for third part reimbursement. The proper CPT codes for all aspects of use are listed in our <u>Reimbursem</u> 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 <u>surrogate marker</u> (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 IntelligenceSM 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

http://rxfiles.net/products_ids_info.html

5/8/01

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 and 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, effectiv 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 ral 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

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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 may 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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http://rxfiles.net/products ids info.html

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IDS BCA ek us a Question

The Intelligent Dosing System[®] FAO

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http://rxfiles.net/faq.html

5/8/01

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progression to a therapeutic outcome as a percentage of desired response achieved.

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5/8/01

EXHIBIT 2.3 PRODUCT LITERATURE

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WEVE DISCOVERED THE DOSE RESPONSE CURVE FOR EVERY DRUG. Records Placessed under SPIA/Repuest # 2015/8339/Repeated by CORH on 11 # 2015

REVOLUTION OF DUTIER DE LA COMPANIE SA MEN. KND DUSING

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
- · PRODUCES UNIFORM RESULTS FROM MULTI-CENTER TRIALS

- DOSE TO ANY SURROGATE MARKERS, OBJECTIVE OR SUBJECTIVE, POSITIVE OR NEGATIVE
- * CREATEST EXPERTISE AVAILABLE FOR EACH DOSE CALCULATION
- GRADED PRESCRIBER CASE SIMULATIONS
- THERAPEUTIC INTERCHANGER

The Refiles 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

SECTION 3 EQUATION FORMULA

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118





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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118





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SECTION 4 HAZARD ANALYSIS

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SECTION 4: HAZARD ANALYSIS



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SECTION 5 SOFTWARE REQUIREMENTS SPECIFICATIONS

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SECTION 5: SOFTWARE REQUIREMENTS SPECIFICATIONS

	Hardware Platform	
(b) (4)		
	Des succes I and page	
(b) (4)	Program Language:	
	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 IDSTM 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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(b) (4)

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

Generic Formulae T for Any Agent w Doser – Stochastic (b) (4) Open Loop

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

EXHIBIT 5.2 SOFTWARE REQUIREMENTS SPECIFICATIONS

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

SRD = Page #		FDA 50L - Guidance for the Content of Premarket
Or document	1	Submissions for Software Contained in
named		Medical Devices
	Section3. Document	ition in a Premarket Submission
	Submis	sions for Software Contained in
Separate Document	3.1 Level of Concer	n,
	Medic	al Devices
Substantiation of	Provide	the level of concern of your cofficience and the amagenting actionals (as 0 and a 0 a distance of a distance of a distance of the distance of
sales claims	is maio	and where here on concern of your software, and the supporting rationale (see Section 2 for details). If the level of concern
document	recomm	and you have not previously submitted a premarket submission for this type of device to ODE, it is strongly
	2 2 Approach Pacom	number that you contact the appropriate division prior to making the submission
	2.2.7 Operation Proce	The second s
	2 Dow	
	J. DUC: death a	s the device software control treatment delivery, such that an error or malfunction with the delivery could result in
	ucaui u	I serious injury?
	Identifi	callon of Hazards - SRD pages 46-50
	Hazaro	s resolution - SRD pages 52 - 57
44.04	3.2 Soltware Descri	ption
14-21	Provide	a comprehensive overview of the device features that are controlled by software, and describe the intended
	operatio	anal environment.
0.40	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
	softwar	e NOT do? How does the user interact with the software? What software functions can be controlled or modified
	the user	, and which are unchangeable? Which, if any, of the software features have hardware over-rides or backups?
	This inf	formation 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
l.	3.2.2 Operational Env	ironment
	The des	cription of the intended operational environment should include the following:
4	program	uming language
4	hardwar	e platform
4	operatin	g system (if applicable)*
None	use of C	off-the-Shelf components (if applicable)*
None	<u>* If you</u>	r device uses Off-the Shelf components, please refer to FDA's (draft) Guidance for Off-the Shelf
	Softwar	re Use in Medical Devices (see Appendix C.6).
	3.3 Device Hazard A	nalysis
	Submiss	sions for any level of concern should contain a device hazard analysis that takes into account all device hazard
	associat	ed with its intended use, hardware, and software. The hazard analysis should include the following:
46, 57	a) the ha	azardous event;
46, 57	b) level	of concern of the hazard;
46, 57	c) the ca	use(s) of the hazard;
46, 57	d) the m	ethod of control:
46, 57	e) correc	tive measures taken, including aspects of the device design/requirements, that aliminate and the second second
	hazardou	is event, including a discussion of their approximate according and a second and the second according a discussion of their approximate and
46, 57	f) testing	to demonstrate that the method of control use implemented expects
50	This info	Structure and the include of control was implemented correctly.
1	careful to	o include all foreseeable hazards including those resulting fores intentional analysis, manufacturers should be
50	There an	e times when a fault tree analysis of the software is useful. For each identify 11
	carried o	ut to discover the conditions which might cause that heard (and (a) the second for the conditions which might cause that heard (and (a) the second for the s
	which is	a fault tree analysis which involves identifying the undering the undering the state of a fault tree analysis which involves identifying the undering the undering the state of the state o
	discover	the possible causes of the bazard
3	4 Software Require	ments Specification (SDS)
1-82	The Cold	Ware Decurrements Creation Laws of the second
	narforme	wate requirements Specification documents the requirements for the software. This typically includes functional,
	pertorilla	in a SPS include:
9	a) hereter	ara ono moudo.
	a) nardw	are requirements, including microprocessors, memory devices, sensors, energy sources, safety features,
		icanons, cu.;
1	o) progra	mming language and program size(s);
	c) interfa	ce requirements, including both communication between system components and communication with the user
1	(e.g., pri	iters, monitors, keyboard, mouse, etc.);
44 00	d) softwa	re performance and functional requirements, examples of which include:
14 - 29	- algorith	ms or control characteristics for therapy, diagnosis, monitoring, alarms, analysis, and interpretation (with full text
	reference	s or supporting clinical data if necessary),
4 4 m m m m m m m m m m m m m m m m m m		
14 - 29	- device l	imitations due to software,

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14 - 2	9 - error and internet handling
14 - 2	9 - Guit detection toleman and measure characteristic
14-2	- safety requirements
14-2	- time and requirements
14 - 2	- intring and includely requirements,
none - majo	For a minor concern divisio it is usually surgely and in the state of
	moderate and reduces a this usually sufficient to provide only the functional requirements section from the SRS. For
	3.5 Architecture Design Chert
4	B End the second charter the second s
	rol minor lever 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
	autilicitude at the third container evel.
	The inductate and major concern devices, the chart should be more detailed, although still focused at the functional level.
	fulfiling the column and an include a list of functional modules, and a description of the role that each module plays in
	3 6 Desten Specification
1-8	
	The souware 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
1 ·	have an increasing decisions. The software design specification should include documentation of the elements listed
6.7	Software Real and the second s
g	 Software Requirements Specification, including predetermined criteria for acceptance of the program;
40	Lorenze A as here
Jan-82	• rizzaro Analysis;
	Systems documentation (context in which the program is intended to function, e.g. systems documentation narrative
4	Underst unagram;
18, 24	
19-22	Longia (Dariand structures accorded)
30,74	Data Structures and data form discrete restriction steps);
20-23,28	 Definitions of variables (control and deta) and description of the state of the sta
None	Error and alarm messages
See Overviews	Supporting software (e.g. operating systems, drivers and other and the set in the set is a set of the set
PMS,VMS, DMS	
59,71	 Communications links (links among internal modules of the software, links with the supporting software and links
70.76	with the hardware); and
70,70	 Security measures (both physical and logical security).
PMS	3.7 Traceabinty Analysis
	Provide a traceability analysis or matrix which links requirements, design specifications, hazards, and validation.
	for determining these activities and documents is essential. This document acts as a map, providing the links necessary
	ordination of the sector of th
	through the information included in the start scheme, appropriate information should be provided to guide the review
	3.8 Development
None Needed	For moderate and major opposed during the second state of the seco
	software development life cycle plans. The summary struct is in it.
	software development life cycle activities. Also for moderne
	configuration management and maintenance plans
12	In addition, for major concern devices, the submission should include an another that the
	generated during the software development process as well as the configuration mentation and the control/baseline documents
	3.9 Validation, Verification and Testing
46-51	Software verification involves a systematic application of various analyzes, application of various
	software and its supporting documentation at each stare of the software devices revenue on the software devices and testing of the
	requirements specified for that stage have been fulfilled. Software validation uses similar contained to the
	further to assure, to the extent possible, that the finished device (with its incompared optimal analytical techniques, but goes
	intended use and will be reliable, and safe.
ł	The following test information should be provided:
none	a) for a device in which the software is considered of minor level of concern-
	- 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-
	- a description of the verification activities at the unit, integration and system level
	- a system level test protocol includion and (2011) is a second of the system in the
	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:
46-51 50	 c) for a device in which the software is considered of major level of concern: - a description of the verification activities at the unit, integration and system level.
46-51 50 51	 c) for a device in which the software is considered of major level of concern: - a description of the verification activities at the unit, integration and system level, - unit, integration and system level test protocols including pass/fail criteria, test report, summary, and test results

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check lists provide	All testing information should include the version and revision identifiers for the software and a discussion of testing results
by JDK and MC	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	- <u>qualification of off-the-shelf software (see Appendix C.6)</u>
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 Unresolvéd 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	For all levels of concern, the submission should include the release version number and date for the software that will be
/4	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	Inere are a vanety of tile cycle models, such as: waterial, spiral, evolutionary, incremental, top-down functional decomposition (or starwise refinance) symptometike professional decomposition of the second starwise refinance of
	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,
	4.2 Requirements Analysis and Smathagement activities to life cycle activities.
6	Barty in the during design process, there is an activity which identifies and each as a sufficience of the first state of the state of
	the set of
	software it is important to define the role of the coffusion in the during of this is in a proving a with mean the role of the coffusion in the during at this is martiaulte with mean the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at the role of the coffusion in the during at the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at this is the role of the coffusion in the during at the rol
	functions. During this requirements activity the functions to be performed controlled or monitorial by the software are
	documented. Software cuality characteristics such as human factors functional characteristics response times output
	safety requirements, etc., are defined along with accentance criteria
46	Software safety requirements are derived from the preliminary barred analysis and opening risk management estimities
	requirements are indicated throushout the life cycle invices. Any hazardous software finations are identified and builds, as
	traced to be able to show subsequent mitigation of the risk associated with those functions to an accentable lawal
	4.3 Risk Management
46	Rick analyzement is a combination of rick analyzis and rick control estimation. Rick and here in and the standard the stan
	associated with the use of the device and risk analysis and tak control activities. Nisk analysis is used to estimate the risk
	manufacturer to have a risk management risk control is used to minigate the risk to an acceptable fever, it is normal tor a
	These activities are oppoint throughout the device life cycle. Risk analyses shuld be performed for the device as an estimate
	as well as major components/subsystems. A component exchanges should be despense to that risk the solutions for the solutions
	electronics, biomaterials and so forth, can be effectively integrated and analyzed at both the device level and at the
1	subsystem level.
	Several national and international consensus standards, such as those cited in Appendix B, can assist manufacturers during this
1	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 cofference. The colorial of a constant of the cons
-	the curve of the random 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

	1.2.1 Disk Analysis Activities
1	4.5.1 KISK ADAILYSIS ACTIVITIES
46	Kisk analysis includes nazard analysis and fish continuous. Hazard analysis provide commistances. Hazard analysis is
1	device hazards. Potential device nazards are identified areadones it should begin early in the life cycle, as requirements are established,
	conducted in accordance with established proceedings, it anothe effectiveness of hazard mitigation and whether any new
	and should be updated as development progresses, we assess the effect on the following: patients, operators,
	hazards have been introduced. Device nazards should be considered for their effect on the following, particular,
	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 or an
	following areas: human factors, hardware faults, software faults, integration errors, and environmental conditions. A three
	of methods can be used to perform the hazard analysis (e.g. tault tree analysis, tailure 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
1	purposes of this document, a software related hazard is defined as any device hazard that has its initiating cause of a major
	contributing cause in software. For software related hazards, the hazard analysis documentation should identify traceaonity
	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
1	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	 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. Protocold is a second second to a second the protocold is a second to be protocold in the protocold is a second to be appropriate to appropr
	determination is made as to whether or not the risk control measures introduced any new nazards, in so, the process is reported.
	Reterming to Figure 4, sees 2 difficult and represent to recomplications 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:
4	1. a description of the identified hazard;
Substantiation o	2. the severity level of the hazard (major, moderate, or minor);
sales claim	s de la constante d
documen	t de la construcción de la constru
operational range	 the specific software cause of this hazard, so it can be traced to the specific location in the software;
4	6. 4. risk control method employed;
49, 50, 5	5. test or verification method used to confirm the risk method employed; and
	6. severity level of the hazard after the risk control method has been implemented.
4	- what the estimated severity of each hazard is and how it was categorized;
5	- what risk reduction and mitigation techniques were implemented and how their effectiveness was assessed; and
5	- testing and evaluation demonstrating the implementation of the safety features.
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Pages 207 through 288 removed.

EXHIBIT 5.3 Documentation of Improvement: RxFiles Corporation Systems Modification Log



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Questions? Contact FDA/CDRH/OCE/DID at CDRH/F@STATUS@fda.hhs.gov or 301-796-8118

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOI&TATUS@fda.hhs.gov or 301-796-8118





Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118



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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.

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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.

		[] 이상 : 2013 - 2014 - 2017 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014 - 2014	ا الیتشید 1967 - 1990 (1993) 1969 - 1990 (1993)
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inception used (I COM_LECTURE DCIAIK		U.UU
iject Info Project Detail Process h	ito Task Into		
Design Specifications			
Design Specifications	Design Approver JMcMichael		
Design Specifications Design Approval Date Review Approval Date Review Specifications	Design Approver JMcMichael Review Approver Michael D		

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Project 1007		an e det			
Project Details					
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ect Info Project Detail Process I	nfo Task Info				
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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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P	roject De					
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SECTION 6 DESIGN SPECIFICATIONS

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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



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EXHIBIT 6.2 DEVELOPMENT AND PROGRAMMING STANDARDS

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EXHÍBIT 6.3 HAZARD ANALYSIS

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EXHIBIT 6.4 SYSTEMS DOCUMENTATION

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The RxFiles Corporation Version Management System

Focus Statement

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

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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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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 (IDSTM Calculator Application) or as a selection in a Agents Doser Suite (IDSTM 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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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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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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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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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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Overview

Introduction

The RxFiles Corporation's **Project Management System (PMS)** was instituted to <u>register</u>, <u>document and track</u> the Project Initiation, Needs Analysis, Design, Construction, Implementation, Bugs Assessment, System Modification and Modification Implementation <u>stage completion</u> <u>history</u> 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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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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FOI - Page 351 of 437
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 subtherapeutic 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 <u>register and track</u> White Papers, Systems Supporting Documentation, Research Papers and Associated written errata, together with their individual <u>revision history</u>, generated by the Firm for general release to the Professional Health Care Industry.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Overview

Introduction

The RxFiles Corporation's **Document Management System (DMS)** was instituted to <u>register and track</u> White Papers, Systems Supporting Documentation, Research Papers and Associated written errata, together with their individual <u>revision history</u>, generated by the Firm for general release to the Professional Health Care Industry. The **Document Management System (DMS)** is comprised of a data repository, graphical user interface and reports generator. The **Document Management System (DMS)** 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.



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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

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

FOI - Page 356 of 437

Overview, Continued

The Document Management System directs the itemization and crosscorrelation 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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EXHIBIT 6.5 HARDWARE TO BE USED

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXHIBIT 6.6 PARAMETERS FOR PROGRAM

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXHIBIT 6.7 LOGIC

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EXHIBIT 6.8 DATA STRUCTURES AND DATA FLOW DIAGRAMS

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EXHIBIT 6.9 DESCRIPTION OF VARIABLES

3.6 Description of Variables and where they are used.

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



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 6.10 SUPPORTING SOFTWARE

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 377 of 437



Questions? Contact FDA/CDRH/OCE/DID at ODRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXHIBIT 6.11 SECURITY MEASURES

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118. FOI - Page 379 of 437

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SECTION 7 ARCHITECTURE DESIGN CHART

EXHIBIT 7.1 ARCHITECTURE DESIGN CHART

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SECTION 8 TRACEABILITY ANALYSIS
SECTION 8: TRACEABILITY ANALYSIS

Traceability Analysis: Reference Exhibit 8.1 8.1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118



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EXHIBIT 8.1 TRACEABILITY ANALYSIS

The RxFiles Corporation Project Management System

Focus Statement

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

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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 SystemTM (IDSTM) 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.

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

Current Business Process - Evaluate Trends Analysis



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System Requirements Definition Confidential -

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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5/1/2001

Activity Requirements - Reconcile Best Fit with Patient Data, Continued

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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.

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- 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

- 9.1 Software Development Life Cycle Summary Reference Exhibit 9.1
- 9.2 Life Cycle Models and Methodologies Reference Exhibit 9.2
- 9.3 Requirements Analysis and Specifications Reference Exhibit 9.3
- 9.4 Risk Management Reference Exhibit 9.4
- 9.5 Documentation Reference Exhibit 9.5

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EXHIBIT 9.1 SOFTWARE DEVELOPMENT LIFE CYCLE SUMMARY

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 398 of 437

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EXHIBIT 9.2 LIFE CYCLE MODELS AND METHODOLOGIES

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118. FOI - Page 400 of 437

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EXHIBIT 9.3 REQUIREMENTS ANALYSIS AND SPECIFICATIONS

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118



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EXHIBIT 9.4 RISK MANAGEMENT

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4.3 Risk Management

- 4.3.1 4.3.2
- 4.3.3

See Documentation of all of our Tests at:

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Activity Requirements - Evaluate Special Needs and Quantities

Overview

This process consists of evaluating the risks or hazards associated with of the use of the IDSTM 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 IDSTM. 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.

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46 System Requirements Definition - Confidential - 5/1/2001 Questions? Contact FDA/CDRH/OCE/DID at CDRH-FQISTATUS@fda.hhs.gov or 301-796-8118 ጋገ ዓ FOI - Page 411 of 437

Activity Requirements - Evaluate Special Needs and Quantities, Continued

The current process for Evaluate Special Needs and Quantities is shown below. **Current business** process - Evaluate Special Needs and Current Business Process -**Evaluate Special Needs and Quantities** Quantities **Begin Quality Control Re** Repeat this process for each Agent Process of IDSTM Agent Dose Iter Developmental Bench Testi Doser executable as well as for each operating system deliverable Complete Register Version to on N tterative Development Cycle Sy **Clinical Practitioner's Expe** e Developer's Experience Clinical Particios Service Conduct Inle Hazard Review Engineering Evalu **Clinical Evaluation** Document Rev Rectify or Modily as ults in Project ment Sva ase Version to 20 Version Managem System Process Complete continued on next page

 5/1/2001
 System Requirements Definition - Confidential 47

 Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
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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.



continued on next page

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 System Requirements Definition - Confidential 49

 Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
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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 TM 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

Attention!	
The IDS is reasoning. based sole this softwa	not a substitute for clinical No medical decision should be ely upon the results provided by re program.
	IUnderstand

The IDS[™] is an aid for trained clinicians based upon data properly entered by the user. The calculator is intended only as a guide. Final drug dose recommendations for a patient must be made only after careful consideration of the full clinical status of the patient. Use of the IDS[™] other than as authorized by The RxFiles Corporation(SM) is prohibited.

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**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 419 of 437

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



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oo@ida.iiiio.ge



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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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PREDICATE PRODUCT COMPARISON

294 Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118. FOI - Page 427 of 437

SECTION 11: PREDICATE PRODUCT COMPARISON

11.1 Intended Use:

The Intelligent Dosing System (IDS)TM is a three-part software suite comprised of DoseRxTM, InterchangeRxTM and PracticePrescribeRxTM. The DoseRxTM is designed for use by trained clinicians to calculate any individual patient's optimal next dose for any given agent. The InterchangeRxTM 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 property 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 E K Number	quivalence Comparison Table: IDS TM Dosing System	PDT DoseCalculator 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 TM is a three part software Suite comprised of DoseRx TM , 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 TM , a graded prescriber stimulator. All IDS TM software can be accessed with Pam 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 d	levice is not required to be sterile		

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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

EXHIBIT 11.1 PREDICATE PRODUCT INFORMATION

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 FOI - Page 430 of 437 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration 9200 Corporate Boulevard Rockville MD 20850

OCT 2 4 2000

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

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 <u>Code of Federal Regulations</u>, 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 <u>Federal Register</u>. 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.

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Page 2 - Mr. Frank Tighe

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,

h M Melhers

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

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Records Processed under FOIA Request # 2015-8339; Released by CRHOP 19-2015



K00041P

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

(Division Sign-Off) Division of General Restorative Devices 510(k) Number _______ K0004/18 Over-The-Counter Use

(Optional Format 1-2-96)

301

 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

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 <u>Hemotech Inc</u> .	Dose Calculator Integrity Medical Software	PDT DoseCalculator <u>RetinaLabs.com</u>	
Software Based	x	X	x	
BSA Calculation	X		X	
Dose Calcula	ttion	x	X	

Sterility

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The Device is not required to be sterile.

Page 2 Summary

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FDA > CDRH > PMIN Search

Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

- Center for Devices stid Radiolo U.S. Food and DP Premarket Other MAUDE PMA Classification 510(K) Listing Notification disclaimer | site map | more 510(K) information | a E Star Corri Return to Search CALCULATOR, DRUG DOSE 三の人間の市 **Device Classification Name** 868.1890 **Regulation Number** K000418 510(k) Number ំពោះក្រើនំ PDT DOSECALCULATOR, MODEL 80000 **Device Name RETINALABS.COM** 1 **1776 PEACHTREE STREET** Applicant 200 NORTH ATLANTA, GA30309 FRANK TIGHE Contact NDC **Product Code** Sparish FD. **Date Received** 02/08/2000 10/24/2000 **Decision Date** SUBSTANTIALLY EQUIVALENT Decision Classification Advisory Committee General & Plastic Surgery General & Plastic Surgery **Review Advisory Committee** Statement/Summary/Purged Status Summary only SUMMARY/Approval Letter SUMMARY Traditional Type **Reviewed by Third Party** No

(Database Updated May 7, 2001)

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=337 5/11/2001 Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118 305 FOI - Page 435 of 437 Records Processed under FOIA Request # 2015-8339; Released by CDRH on 11-9-2015

OCT 2 4 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

Page 1 Summary

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FDA/CDRH IMAGING SYSTEM

Page Count Discrepancy Information

Page #6 was moved belind page #103 for document order. The page after page 124 was numbered 126. Upages after the page marked 294 were not numbered.

Verifiers Initials