

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20931**

**CHEMISTRY REVIEW(S)**

D. Proeder

JAN 26 1999

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

**NDA #: 20-931**

**DATE REVIEWED: 1/6/99**

**REVIEW # 1**

**REVIEWER: Stuart Zimmerman**

<b>SUBMISSION TYPE</b>	<b>DOCUMENT DATE</b>	<b>CDER DATE</b>	<b>ASSIGNED DATE</b>
ORIGINAL (PRE-)	25-NOV-97	26-NOV-97	01-DEC-97
NC	04-MAR-98	Transfer of NDA ownership notice	
ORIGINAL (Full)	09-MAR-98	09-MAR-98	11-MAR-98
AMENDMENT	20-MAY-98	21-MAY-98	22-MAY-98
AMENDMENT	03-JUN-98	04-JUN-98	06-JUN-98
AMENDMENT	13-OCT-98	14-OCT-98	16-OCT-98
AMENDMENT	27-OCT-98	28-OCT-98	29-OCT-98
AMENDMENT	12-NOV-98	13-NOV-98	15-NOV-98
AMENDMENT	23-NOV-98	24-NOV-98	25-NOV-98
AMENDMENT	24-NOV-98	25-NOV-98	26-NOV-98
AMENDMENT	07-DEC-98	08-DEC-98	09-DEC-98

**NAME & ADDRESS OF APPLICANT:** Pfizer Pharmaceuticals Production Corporation Limited.  
Street Address: Ringaskiddy  
City, State, ZIP - County Cork, Ireland

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Tikosyn
<u>Established:</u>	dofetilide
<u>Code Name/#:</u>	UK-68,798
<u>Chem. Type/Ther. Class:</u>	1S

**PHARMACOL. CATEGORY/INDICATION:** Class III Antiarrhythmic Agent

**DOSAGE FORM:** Capsules

**STRENGTHS:** 0.125, 0.25 and 0.5mg

**ROUTE OF ADMINISTRATION:** Oral

**Rx/OTC:**  Rx  OTC

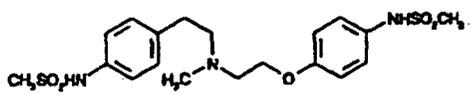
**SPECIAL PRODUCTS:**  Yes  No

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WT.**

*N*-[4-(2-(2-[4-(methanesulphonamido)phenoxy]-*N*-methylamino)ethyl)phenyl)methanesulphonamide

Structural Formula

The structural formula of dofetilide is given below:



Molecular Formula and Molecular Weight

**Molecular Formula of Dofetilide:** C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>

**Molecular Weight of Dofetilide:** 441.6

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status (From cross-checks)	Review Date	Letter Date
IND	dofetilide	Pfizer	Adequate	Code 1	N/A
DMF	Plastic Bottles		Adequate	"	N/A
DMF	Plastic Bottles		Adequate	"	N/A
DMF	Plastic Bottles		Adequate	"	N/A
DMF	Plastic Bottles		Adequate	"	"
DMF	Plastic Bottles		Adequate	"	"
DMF	Plastic Bottles		Adequate	"	"
DMF	Plastic Bottles		Adequate	"	"
DMF	Bottle Closure		Adequate	"	"
DMF	Bottle Closure		Adequate	"	"
DMF	Bottle Closure		Adequate	"	"
DMF	Bottle Closure		Adequate	"	"
DMF	Liner		Adequate	"	"
DMF	liner		Adequate	"	"
DMF	liner		Adequate	"	"
DMF	Desiccant		Adequate	"	"
DMF	Aclar Blister		Adequate	Code #2	N/A
DMF	Foil Backing		"	"	"
DMF	"		"	"	"
DMF	"		"	"	"
DMF	Foil Blister		"	"	"
"	Foil Backing		"	"	"
DMF	Foil Backing		"	"	"
DMF	Foil Backing		"	"	"
DMF	Capsule Shell (BSE )		"	Code# 3	"
DMF	Capsule Shell (BSE)		"	Code #4	"

DMF # (Continued)	Subject (continued)	Holder (Continued)	Status (continued)	Rev Date Continue	Ltr Date continued
DMF	Black Ink		"	Code #3	"
DMF		Pfizer	Inspection is Adequate	No need to review	N/A
DMF	Contract Packager		"	Code #3	"
DMF	Contract Packager		"	Code #3	"
DMF		Pfizer	N/A	No need to review	N/A

**Code #1** These are common DMFs that have been indicated to offer no particular potential problems since they are currently used across a wide number of approved NDAs by the applicant. It is assumed that their evaluative review status continues to be adequate without checking out each DMF.

**Code #2** This grouping of DMFs was assessed using the evaluative tools available (e.g., electronic file system with Excalibur search engines to check the regulatory review status across different NDAs for common packaging components). Then, a decisional basis for suitability was documented in the packet entitled: "Notes To File About Packaging DMFs for NDA 20-931" which was filed in the HFD-110 Div File for NDA 20-931 on 6/12/98. This approach was taken to streamline the evaluative process in anticipation of the need to rapidly reach assessment outcome results for a drug product that potentially would be given a priority rating and hence be placed on a fast track schedule. It was found that the needed supporting information was available -as determined by this *stop-gap* measure. In the event that a more conventional review would be needed to provide for an actual review to be filed in a DMF and hence more available to other reviewers, then it is planned to complete such a formal review in the future - perhaps when the next follow-up review is prepared for this NDA 20-931.

**Code #3** This code deals with DMFs that are not considered to be problematic since they relate to well-known and established process operations. Some will be evaluatively revisited under the next Chemistry Review #2 (e.g., DMFs

**Code #4 -DMF** This was added after the NDA was submitted and deals with the use of the hard gelatin capsule manufacture by

In this regard, the Chemistry Review of 10/8/92 indicates the DMF is satisfactory. The representative, Mr. Chris Kotevich, was contacted on 12/16/98 and requested to update their LOA to reflect the correct Corporate name for the applicant since it is the Ringaskiddy, Ireland name. This will be done. There is no other reason to provide for an additional Chemistry Review for this DMF. Also, there is provided a FAX of 12/18/98 from Chris Kotevich that documents the firm's compliance with the FDA/BSE regulations

**RELATED DOCUMENTS:** INDs

**CONSULTS:** None needed

**REMARKS:**

A number of issues were brought to the attention of the applicant as the review was ongoing. Some of these matters were documented as facsimiles. The content of these concerns are normally repeated in the applicant's response to provide for a sense of continuity.

**FDA/CMC PRE-APPROVAL COMMUNICATIONS TO THE APPLICANT**

<b><u>Type/Date Sent</u></b>	<b><u>Issue Definition</u></b>	<b><u>Draft Resolution Status*</u></b>
FAX 1/12/98	Pre-approval Inspection	Inspection undertaken
FAX 4/30/98	Stability Requests	Pending updated data
FAX 4/28/98	Photo-stability (MV)	Additional questions
FAX 5/4/98	Excipient Controls	Response is adequate
FAX 5/5/98	Methods Validation	Matter resolved
FAX 5/11/98	CBE protocol issues	Matter resolved for now
FAX 5/12/98	Packaging (child resistant)	Resolved
Mail Packet-6/11/98	CBE Protocol Guidance	Resolved /NDA approval
FAX 10/7/98	Innerseal Protocol data	Resolved
FAXA 12/10/98 (SZ)	Container/closure issues	Outstanding as of 1/6/98

**ONGOING EVALUATIVE CONCERNS:** Several CMC issues need additional attention and will be covered in the next Chemistry Review #2. These matters are outlined here. They will be voiced to the applicant for resolution. (1) 500 count designation - submission of 11/23/98), (2) Need to provide revised interim dissolution specifications, (3) Plans to use (4) Need for Expressing the expiration date in the How Supplied section of the package insert, (5) Need to include the "cold form foil" blister -not just Aclar blisters - in the How Supplied section, (6) Need to provide revised labels in final printed form.

**CONCLUSIONS & RECOMMENDATIONS:** This NDA is considered to be approvable from the standpoint of the chemistry and manufacturing controls issues involved pending the satisfactory inspection of the firm's facility in Puerto Rico and the submission of additional information - above ongoing concerns and issues as expressed in the Fax of 12/10/98 from the reviewer. The validation of the applicant's analytical methods is pending and does not impact on the NDA approval process.

cc.

Org. NDA 20-931

HFD-110/Division File

HFD-110/SZimmerman 1/6/99

HFD-110/PM DRoeder

HFD-110/KSrinivasachar

HFD-810/CHoiberg, DNDC1 Director

R/D Init by: Ksrinivasachar 1/12/99

**Filename#1:** (relates to the bulk drug substance): Dodrug2c(Pages 1-25) **Filename#2** (relates to drug product):DOFPDT, (Pages 26-69) under My Documents

*JSI*  
Stuart Zimmerman, Ph.D.

*JSI*

*1-26-99*

Koeder

FEB 23 1999

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
Continued Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-931

**DATE :** 2/22/99

**REVIEWER:** Stuart Zimmerman

**ADDENDUM TO CHEMISTRY REVIEW #2 FOR NDA 20-931:**

**NAME & ADDRESS OF APPLICANT:**

Pfizer Pharmaceuticals Production Corporation Limited.  
Street Address: Ringaskiddy  
City, State, ZIP - County Cork, Ireland

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Tikosyn
<u>Established:</u>	dofetilide
<u>Code Name/#:</u>	UK-68,798
<u>Chem.Type/Ther.Class:</u>	1S

**PHARMACOL. CATEGORY/INDICATION:**

Class III Antiarrhythmic Agent

**DOSAGE FORM:**

Capsules

**STRENGTHS:**

0.125, 0.25 and 0.5mg

**ROUTE OF ADMINISTRATION:**

Oral

**Rx/OTC:**

Rx  OTC

**SPECIAL PRODUCTS:**

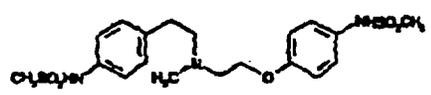
Yes  No

**CHEMICAL NAME, STRUCTURAL FORMULA**

The chemical name for dofetilide is:  
N-[4-[2-[methyl(2-[4-[(methanesulfonyl)amino]phenoxy)ethyl]amino)ethyl]phenyl]-methanesulfonamide.

**Structural Formula**

The structural formula of dofetilide is given below



**Molecular Formula and Molecular Weight**

**Molecular Formula of Dofetilide:** C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>

**Molecular Weight of Dofetilide:** 441.5

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1

**CONTINUED DISCUSSION:** Several topics are covered to Help account for Outstanding Questions:

**STABILITY EVALUATIVE REMARKS CONCERNING WATER CONTENT LEVELS:** It is CONSIDERED TO BE NECESSARY TO DEAL WITH THE MOISTURE CONTENT ISSUE AGAIN TO HELP CLARIFY THE POTENTIAL PROBLEM TO HAVE DRUG PRODUCT FAILURES BASED ON VALUES THAT MAY OCCUR ON EXTENDED STABILITY TESTING. THE APPLICANT'S SPECIFICATION LIMIT IS<sup>1</sup> % . CONCERNING THE WATER CONTENT DATA RESULTING FROM STUDIES CONDUCTED AT 30°C/60%RH AFTER 12 MONTHS, IT IS NOTED THAT THERE ARE NO FAILURES IN ANY OF THE PACKAGING CONFIGURATIONS AND THERE IS A COMFORTABLE MARGIN OF AT LEAST % FOR THE BATCHES STUDIED BEFORE FAILURE AT % . THE FIRM'S 18 MONTH DATA SHOWS NO FAILURES FOR THE 30°C/60%RH CONDITION AS GIVEN IN THE 12/7/98 SUBMISSION. HERE, THE WORST CASE VALUE WAS % AT THE 9 MONTH INTERVAL FOR THE STABILITY LOT PROVIDED ON PAGE 147. IN THIS CASE, THE VALUES AT 12 AND 18 MONTHS HAD DECREASED TO VALUES OF % . SUCH A SIMILAR PEAKING EFFECT AT 9 MONTHS IS ALSO SEEN IN OTHER RELATED DATA. HENCE, NO FIRM TRENDING EFFECT CAN BE ESTABLISHED THAT MAY PREDICT A CERTAIN FAILURE RATE BASED ON A KNOWN TRENDING EXPERIENCE. SO, THERE IS NO KNOWN CONTROL PROBLEM FOR MOISTURE CONTENT AT THIS TIME.

**STORAGE STATEMENT CONSIDERATIONS:** THERE ARE SEVERAL CONCERNS RELATING TO THE APPLICANT'S WISH TO CHANGE THEIR STORAGE STATEMENT IN THEIR AMENDMENT DATED 2/3/99 TO "STORE AT CONTROLLED ROOM TEMPERATURE , 15° to 30°C (59 - 86°F)" FROM "STORE AT EXCURSIONS PERMITTED TO 15-30°C (59-86°F) [SEE USP CONTROLLED ROOM TEMPERATURE] - AS PREVIOUSLY CHANGED BY FDA SUGGESTION. SINCE THE FIRM WANTS TO USE THE 30°C STATION, THERE ARE A NUMBER OF PROTOCOL ISSUES THAT NEED TO BE CHANGED: (1) CONCERNING THE STABILITY PROTOCOLS CURRENTLY IN PLACE FOR CONDUCTING TRIALS FOR THE COMMERCIAL BATCHES, THERE IS NEED FOR REVISION TO INCLUDE THE 30°C/60%RH TEST CONDITION, (2) CURRENTLY CONDUCTED TRIALS THAT DO NOT INCLUDE THIS STATION OUT TO THE EXPIRATION DATE ALSO NEED TO BE REVISED SUCH AS THE TRIALS CONDUCTED TO PROVIDE FOR THE PUERTO RICO SITE WHEREBY THERE IS PROVISION TO ONLY CONDUCT TESTING FOR 12 MONTHS AT THIS STATION, (3) THE STABILITY PROTOCOLS DEALING WITH PLACING BATCHES INTO THE ROUTINE STABILITY PROGRAM AS SPECIFIED IN THE VARIOUS INTERCHANGEABILITY PROTOCOLS - AND RELATED CONFIGURATION CHANGES RELATING TO PACKAGING - NEED TO BE CHANGED TO INCLUDE THE 30°C/60%RH STATION EXTENDING THROUGHOUT THE EXPIRY PERIOD. ANOTHER OPTION TO TAKE TO RESOLVE THIS ISSUE IS FOR THE FIRM TO GO BACK TO THE USE OF THE STORAGE STATEMENT THAT THEY HAD ONCE USED WHICH IS THE ONE THAT FDA RECOMMENDED - SEE ABOVE. THIS WOULD THEN MEAN THAT THE PACKAGE INSERT WOULD NEED TO BE AGAIN REVISED AS WELL AS ALL THE LABELING INVOLVED. THE FIRM HAS BEEN ADVISED OF THESE VARIOUS CONSIDERATIONS AND FDA AWAITS THEIR RESPONSE.

**DISSOLUTION SPECIFICATION ISSUE:** IT IS NOTED THAT THE FDA ACTION LETTER WILL NOW CONTAIN A STATEMENT INDICATING THAT THE IT IS EXPECTED THAT AN INTERIM DISSOLUTION SPECIFICATION WILL BE ADOPTED THAT TIGHTENS THE DISSOLUTION LIMIT TO % IN MINUTES.- RATHER THAN AT MINUTES AS INITIALLY PROPOSED. AS NOTED IN THE CHEMISTRY REVIEW #2, THE STABILITY DATA PROVIDED SUPPORTS THIS RESTRICTION. ALSO, IN ACCORD WITH THE SUGGESTIONS GIVEN BY DR. FADIRAN IN HIS BIOPHARMACEUTICAL REVIEW, THERE IS THE POST-APPROVAL ISSUE FOR THE FIRM TO TRY TO REVISE THEIR IN-VITRO DISSOLUTION METHOD SO IT IS BETTER ABLE TO RELATE TO IN-VIVO RESULTS. (E. G., USE OF DIFFERENT MEDIA). ANY SUCH POTENTIAL REVISION WILL NEED TO BE ASSESSED IN TERMS OF ITS ABILITY TO MONITOR CONTINUING STABILITY TRIALS FOR THE FIRM'S ONGOING TRIALS.

**SITE INSPECTION ISSUE FOR PUERTO RICO:** THE SITE HAS BEEN REPORTED TO HAVE HAD AN INSPECTION RECENTLY AND NO 483 WAS ISSUED. THERE IS STILL NO MESSAGE FROM OC ABOUT THE APPROVAL STATUS OF THIS SITE.

**FDA VALIDATION IS PENDING:** THE VALIDATION OF THE APPLICANT'S ANALYTICAL METHODS IS PENDING AND DOES NOT IMPACT ON THE NDA APPROVAL PROCESS.

/S/  
Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931  
HFD-110/Division File  
HFD-110/SZimmerman  
HFD-110/PM DRoeder  
HFD-110/KSrinivasachar  
HFD-810/CHoiberg, DNDC1 Director  
HFD-810/JSimmons DNDC1 Dup Director  
R/D Init by: KSrinivasachar

Filename: Addendum

/S/  
2-22-99

D. Pineda  
1  
FEB 10 1999

DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-931  
**REVIEW #** 2

**DATE REVIEWED:** 2/9/99  
**REVIEWER:** Stuart Zimmerman

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment *	14-DEC-98	15-DEC-98	16-DEC-98
Amendment	11-JAN-99	12-JAN-99	13-JAN-99
Amendment	27-JAN-99	28-JAN-99	30-JAN-99
Amendment	03-FEB-99	04-FEB-99	05-FEB-99
Amendment	09-FEB-99	Open	Open

\* Submission date was not included in the Chemistry Review #1 dated 1/6/99

**NAME & ADDRESS OF APPLICANT:**

Pfizer Pharmaceuticals Production Corporation Limited.  
Street Address: Ringaskiddy  
City, State, ZIP - County Cork, Ireland

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Tikosyn
<u>Established:</u>	dofetilide
<u>Code Name/#:</u>	UK-68,798
<u>Chem.Type/Ther.Class:</u>	1S

**PHARMACOL. CATEGORY/INDICATION:**

Class III Antiarrhythmic Agent

**DOSAGE FORM:**

Capsules

**STRENGTHS:**

0.125, 0.25 and 0.5mg

**ROUTE OF ADMINISTRATION:**

Oral

**Rx/OTC:**

Rx  OTC

**SPECIAL PRODUCTS:**

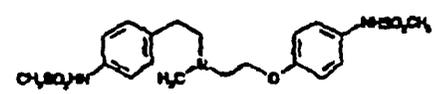
Yes  No

**CHEMICAL NAME, STRUCTURAL FORMULA**

The chemical name for dofetilide is:  
N-[4-[2-[methyl(2-[4-[(methylsulfonyl)amino]phenoxy)ethyl]amino)ethyl]phenyl]-methanesulfonyl]amide.

**Structural Formula**

The structural formula of dofetilide is given below



**Molecular Formula and Molecular Weight**

**Molecular Formula of Dofetilide:** C<sub>27</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>  
**Molecular Weight of Dofetilide:** 441.6

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1



D. Pineda

MAR 5 1999 1

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-931  
**REVIEW #** 3

**DATE REVIEWED:** 3/5/99  
**REVIEWER:** Stuart Zimmerman

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	04-MAR-99	05-MAR-99	05-MAR-99

**NAME & ADDRESS OF APPLICANT:**

Pfizer Pharmaceuticals Production Corporation Limited. (PPPI)  
Street Address: Ringaskiddy  
City, State, ZIP - County Cork, Ireland

**DRUG PRODUCT NAME**

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<u>Chem.Type/Ther.Class:</u>	1S

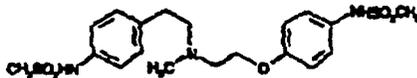
<b><u>PHARMACOL. CATEGORY/INDICATION:</u></b>	Class III Antiarrhythmic Agent
<b><u>DOSAGE FORM:</u></b>	Capsules
<b><u>STRENGTHS:</u></b>	0.125, 0.25 and 0.5mg
<b><u>ROUTE OF ADMINISTRATION:</u></b>	Oral
<b><u>Rx/OTC:</u></b>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC
<b><u>SPECIAL PRODUCTS:</u></b>	Yes <input checked="" type="checkbox"/> No

**CHEMICAL NAME, STRUCTURAL FORMULA**

The chemical name for dofetilide is:  
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**Molecular Weight of Dofetilide:** 441.5

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1

**REMARKS:** This review covers the outstanding issues remaining from Chemistry Review #2. A number of conversations were held between the reviewer and Dr. Murphy and Mr. Dennis Casey to help resolve the storage statement in the labeling for the drug product. These matters were resolved as noted by the applicant's response dated March 4, 1999. This involved several changes in the stability section (e.g., protocol changes for post-approval commercial batches and all ongoing qualification batches in order to provide for data at or beyond the proposed expiry date of 24 months.

The CMC issue of tightening the dissolution specification in terms of shortening the sampling time to minutes from minutes is based on considerations derived from a finalized and documented report from the Division of Clinical Pharmacology concerning the applicant's recent response included in the amendment dated 3/4/99.

The inspection issue for the firm's site in Puerto Rico currently resolved as noted in the report provided

**CONCLUSIONS & RECOMMENDATIONS:** This NDA is considered to be approvable from the standpoint of the chemistry and manufacturing controls issues involved. The firm's methods validations at FDA laboratories is still pending completion but this issue does not impact on the approvable action.

JSI  
Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931  
HFD-110/Division File  
HFD-110/SZimmerman  
HFD-110/PM DRoeder  
HFD-110/KSrinivasachar  
HFD-810/CHOiberg, DNDC1 Director  
R/D Init by: KSrinivasachar

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3-5-99

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SEP 16 1993

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-931  
**REVIEW #** 3

**DATE REVIEWED:** 9/14/99  
**REVIEWER:** Stuart Zimmerman

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	9/8/99	9/9/99	9/13/99

**NAME & ADDRESS OF APPLICANT:**

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Rx  OTC

**SPECIAL PRODUCTS:**

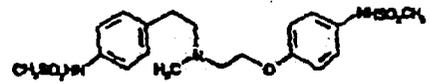
Yes  No

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Molecular Weight of Dofetilide: 441.8

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1

**REMARKS:**

This review is to critically account for the draft labeling provided in reference to the FDA requests.

**ONGOING EVALUATIVE CONCERNS:** The Method's Validation is currently underway since samples have been reported to have been provided to the Philadelphia Laboratory; also samples need to be sent to the FDA at PR – yet no word from this lab.

**CONCLUSIONS & RECOMMENDATIONS:** This NDA is now considered to be acceptable from the standpoint of the chemistry and manufacturing controls issues involved . The validation of the methods is ongoing and will not withhold approval at his time.

**/S/**

Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931  
HFD-110/Division File  
HFD-110/SZimmerman  
HFD-110/PM DRoeder  
HFD-110/KSrinivasachar  
HFD-810/JSimmons DNDC1 Director  
R/D Init by: KSrinivasachar

**/S/**

9-16-99

Filename: NDA20931-CR#3