

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**75203**

**CHEMISTRY REVIEW(S)**

DIVISION REVIEW SUMMARY

ANDA: 75-203

DRUG PRODUCT: Propafenone Hydrochloride

FIRM: Watson Laboratories

DOSAGE FORM: Tablets

STRENGTHS: 150 mg, 225 mg and 300 mg

CONTAINERS: 100's and 500's (for each strength)

CGMP STATEMENT/EIR UPDATE STATUS:

Acceptable dated 7/27/98. LOS-DO recommends approval and intends to conduct a product specific process validation inspection on the subject application.

BIO INFORMATION:

Pending bio-review (of 225 mg strength).

VALIDATION

MV forwarded on 4/4/99. Pending results.

STABILITY

Lot nos. R69296 (300 mg), R77096 (225 mg) and R76996 (150 mg) were placed in accelerated (40°C/75% RH) and room temperature stability studies in the proposed marketing container configurations.

The stability data appended are found to conform to the proposed stability specifications (see table below). Based upon the stability data submitted, the proposed 24 months expiration period should be granted.

The container/closure systems are described.

LABELING

Unacceptable dated 3/5/99. Facsimile to be issued.

STERILIZATION VALIDATION

N/A

SIZE OF BIO/STABILITY BATCHES

Propafenone Hydrochloride is manufactured by \_\_\_\_\_ DMF  
DMF was reviewed and found to be acceptable on March 30, 1998.

150 mg/lot no. R76996/	theo. units/	actual units.
225 mg/lot no. R77096/	theo. units/	actual units.
/300 mg/lot no. R69296/	theo. units/	actual units.

PROPOSED PRODUCTION BATCH

Blank batch record for the intended production batch sizes of (150 mg), (225 mg) and (300 mg) units are included.

SPECIFICATIONS TO BE APPROVED:

Propafenone HCl Drug Substance

<i>Test</i>	<i>Knoll</i>	<i>Watson</i>	<i>USP</i>
Description	white powder	fine, white powder	None
Infrared Spectrum	same as reference	USP(same as reference , prepared as KBr pellet)	<197>
UV Spectrum			None
LOD			≤0.5%
ROI			≤0.1%
MP			171-175°C
PH			5.0-6.2
Specific Rotation			None
Impurity Limit			Single: ≤0.5% Total: ≤1.0%
Assay	✓ %	1%	98.0-102.0%

Notes: 1. Specifications which differ from innovator are emboldened.

has added a particle size distribution specification of NLT 1% LT microns.

DRUG PRODUCTS:

***Propafenone Hydrochloride Tablets Specifications:<sup>1</sup>***

***Innovator(Knoll) vs. Watson***

<i>Test</i>	<i>Knoll</i>	<i>Watson</i>
Description	White, round bi-convex, film coated tablet	Round shaped, white film coated tablets debossed with Watson 582(3)(4) on one side and bisected on the other side V
Identification	exhibits maxima at same wavelength as standard	same retention time
Impurities/Degradation Products	Single: % Total: %	Single: NMT % Total: NMT %
Content Uniformity	1. 10 tabs: 85.0-115.0%, RSD NMT % 2. If 1 tab % and all % and %, if RSD %, or if both, test 20 additional and. 3. 30 tabs: NMT 1 tab or %, all % and %, RSD NMT %	1. 10 tabs: 85.0-115.0%, RSD NMT % 2. 30 tabs: NMT 1 tab %, all % and %, RSD NMT %
Dissolution:  S <sub>1</sub>  S <sub>2</sub>  S <sub>3</sub>	Q: % of labelled amount of DS in 30 min	Q <sup>2</sup> % of labelled amount of DS in 30 min
Assay	% of label claim as C <sub>21</sub> H <sub>27</sub> NO <sub>3</sub> .HCl	% of label claim as C <sub>21</sub> H <sub>27</sub> NO <sub>3</sub> .HCl

- Notes: 1. *The specifications are the same for all three strengths except for appearance, etc.*  
 2. *Specification revised per a Division of Bioequivalence recommendation. Also, the dissolution testing was modified with respect to media, paddle speed and Q value.*  
 3. *Specifications which differ from innovator are emboldened, however, are in compliance with USP monograph.*

STABILITY:

**Watson Propafenone Hydrochloride**

Tests and Specifications	Strength/Package Size		1 Week	4 Weeks	8 Weeks	15 Weeks	
Appearance: Round shaped, white film coated tablets debossed with Watson 582 on one side, bisected on the other side.	150 mg	100's 500's	Meets "	no change " "	no change " "	no change " "	
	225 mg	100's 500's	" "	" " " "	" " " "	" " " "	
	300 mg	100's 500's	" "	" " " "	" " " "	" " " "	
Assay: %	150 mg	100's 500's	97.4% 99.6	98.8% 99.0	97.4% 97.6	96.5% 97.7	
	225 mg	100's 500's	97.5 98.9	102.4 102.2	97.4 97.3	99.1 98.6	
	300 mg	100's 500's	96.8 100.6	98.6 98.3	98.2 97.5	98.9 98.7	
Dissolution: NMT % (Q) in 30 minutes	150 mg	100's 500's	mean range SD 96.0% 91.1-98.2 2.0	97.3% 96.0-98.5 1.0	93.4-97.2- 95.4% 1.5	97.4% 92.9-99.6 2.5	
		500's	mean range SD 93.7 85.5-97.3 4.2	96.8 95.6-97.6 0.8%	95.9 94.9-97.5 1.0	95.5 90.1-99.3 3.9	
	225 mg	100's 500's	mean range SD 96.8 94.5-100.0 1.7	95.1 92.6-98.0 1.9	95.7 94.3-99.6 2.0	93.8 90.9-95.9 1.9	
		500's	mean range SD 95.7 92.7-97.1 1.8	95.8 91.4-98.2 2.4	98.6 97.7-99.2 0.6	93.3 90.7-97.4 2.8	
	300 mg	100's 500's	mean range SD 91.8 88.4-99.1 3.1	93.3 89.9-96.7 2.3	93.4 90.1-97.8 3.2	94.0 88.4-98.0 3.3	
		500's	mean range SD 93.6 89.8-98.0 3.3	93.1 83.5-99.1 6.0	91.5 89.8-93.1 1.5	91.8 88.7-95.8 2.8	
Chromatographic Impurities: DPP <sup>1</sup> NMT % Max Unknown Impurity 0.1% Total Impurities %	150 mg	100's 500's	DPP Max. Unk. Total 0.01% 0.01%	ND 0.01% 0.02	0.02% 0.002 0.02	ND " "	ND " "
		500's	DPP Max. Unk. Total ND 0.01 0.01	ND 0.01 0.01	0.02 0.002 0.02	ND " "	ND " "
	225 mg	100's 500's	DPP Max. Unk. Total ND 0.01 0.01	ND 0.01 0.01	0.02 ND 0.02	ND " "	ND " "
		500's	DPP Max. Unk. Total ND 0.01 0.01	ND 0.01 0.01	0.013 0.003 0.02	0.001 ND 0.001	ND " "
	300 mg	100's 500's	DPP Max. Unk. Total ND 0.01 0.01	ND 0.01 0.01	ND " "	0.01 ND 0.01	0.0005 0.0008 0.001
		500's	DPP Max. Unk. Total ND 0.01 0.01	ND " "	ND " 0.001	0.001 ND 0.002 0.003	0.007 0.002 0.003
Loss on Drying: NMT %	150 mg	100's 500's	2.0% 2.1	1.9% 2.0	2.0% 1.9	2.0% 2.1	
	225 mg	100's 500's	2.0 1.9	1.9 1.9	2.0 1.9	2.1 1.9	
	300 mg	100's 500's	2.0 2.0	2.2 2.2	2.2 2.0	2.2 2.1	

Notes: 1. DPP is N-depropylpropafenone.

RECOMMENDATION:

Recommend approvable letter to issue for Propafenone Hydrochloride Tablets, 150 mg, 225 mg and 300 mg, once Bio and Labeling reviews are deemed to be acceptable.

SIGNATURE:

DATE: April 30, 1999

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 75-203

3. NAME AND ADDRESS OF APPLICANT

Headquarters:

Watson Laboratories, Inc.  
311 Bonnie Circle  
Corona, CA 91720

Manufacturing Facility:

✓ 132 Business Center Drive:  
Manufacturing, Packaging, and Final dosage formulation.  
311 Bonnie circle:  
Research and Development, Analytical and stability testing.

4. LEGAL BASIS for ANDA SUBMISSION

Patent exclusivity has expired - see p.15 of application.

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

Propafenone Hydrochloride

7. NONPROPRIETARY NAME

Propafenone Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

1.	Original submission	9/11/97
2.	Corrections: response to telecon	9/26/97

FDA:

1.	Telephone call re: "loose ends."	9/26/97
2.	Letter of acknowledgment	10/17/97
3.	Labelling review #1 - deficient	11/3/97
4.	Division of Bioequivalence review and facsimile letter - deficient	3/13/98

10. PHARMACOLOGICAL CATEGORY  
Antiarrhythmic

11. HOW DISPENSED  
Tablets

12. RELATED IND/NDA/DMF(s)

<u>Number</u>	<u>DMF #</u>	<u>Firm Name</u>	<u>Function</u>
1.*			NDS supplier
2.			HDPE bottles
3.			Colorant
4.			HDPE bottles
5.			HDPE bottles
6.			Resin colorant/bottles
7.			CR caps
8.			Caps resin
9.			Caps resin colorant
10.			Liners and liner seals
11.			Coils

\*DMF  
Hydrochloride is

DMF. The

DMF for Propafenone

13. DOSAGE FORM  
Tablets

14. POTENCY ✓  
150, 225, 300 mg

15. CHEMICAL NAME AND STRUCTURE

C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>.HCl MW = 377.91

1-Propanone, 1-[2-[2-hydroxy-3-(propylamino)-propoxy]phenyl]-, hydrochloride  
2'-[2-Hydroxy-3-(propylamino)propoxy]-3-phenylpropiophenone hydrochloride  
[34183-22-7]

16. RECORDS AND REPORTS  
N/A

17. **COMMENTS**

This application for the first generic form of propafenone hydrochloride is well assembled and follows the recommended format.

Propafenone is an antiarrhythmic drug of the general class of  $\beta$ -adrenergic antagonists. Specifically, propafenone is a  $\text{Na}^+$  channel blocking agent that is also a  $\beta$ -adrenergic receptor antagonist. It was the subject of a 1971 German patent and currently is marketed by Knoll Pharmaceutical as Rythmol. This submission is the first generic propafenone application.

**Bioequivalence, Labelling Reviews**

The Division of Bioequivalence completed a review some time ago and the deficiencies were sent by telefacsimile letter dated 3/13/98. The review indicated that one of the studies was outside the allowable confidence intervals for  $C_{\text{max}}$  ranges when including a subject which was improperly excluded. Also, the *in vitro* dissolution methodology was found deficient with regard to Q value, dissolution media, and other parameters. This is discussed below with regard to comparison of Watson proposed specifications with those of innovator.

A labelling review dated 9/11/97 identified several deficiencies.

**DMF's**

DMF's authorized in this submission are eleven in number, ten packaging DMF's and one for the drug substance supplied by . . . . . The application contains all the relevant tests, specifications, and procedures for the ten packaging DMF's. The DMF for drug substance, reviewed for the first time, was submitted in April, 1995, and updated October 21, 1997. Aside from lacking a list of authorized firms, the DMF is in good shape and contains all requisite information.

**Process****Exhibit and Production Batch Sizes, Stability**

For the exhibit batches one granulation batch of . . . kg was used for both the 150 mg and 225 mg strengths and one granulation batch of . . . kg for the 300 mg strength. Nominal batch sizes of . . . were prepared for, respectively, the 150,

225, and 300 mg tablets, with actual yields somewhat lower. Intended production batch sizes are 150 mg tablets, 225 mg tablets, and 300 mg tablets.

Propafenone hydrochloride drug substance is a remarkably stable compound to acidic and alkaline hydrolyses, and thermal, oxidative, and irradiative conditions. The studies reported in the drug substance DMF and also in the methods Validation section of this application indicated strongly alkaline hydrolytic and oxidative conditions to be the only studies which resulted in any appreciable degradation. Stability data in the drug substance DMF included 9 months of accelerated stability data and 5 years of long-term data had been collected with no observable degradation.

#### **Innovator Specifications:**

Jim Short, the reviewer responsible for NDA Knoll Pharmaceuticals Rythmol®, supplied the innovator specifications for both the NDS and drug product. See **Table 2A** on page 10 for a **comparison of innovator specifications** for the NDS with Watson proposed specifications and **Table 6A** on page 21 for a similar comparison for the **Finished Dosage Form**.

Significant differences in the proposed Acceptance Specifications for drug substance are impurity limits and assay. For the Finished Dosage Form Controls, significant differences are impurity limits and dissolution parameters, the latter already communicated to the firm in a deficiency letter from the Division of Bioequivalence. See appropriate sections and deficiency comments for additional details regarding these differences.

#### **Deficiencies**

The following minor deficiencies were noted and are discussed in more detail in the appropriate sections:

1. Raw Material Specifications:

a. New Drug Substance, Propafenone Hydrochloride:

The COA supplied by the drug substance supplier on page 394 does not include specification limits for particle size distribution (test

b. Sodium Lauryl Sulfate:

USP 23's 7th supplement deletes the measurement and specification and adds a test and specification for OVI's. The firm's protocol should be revised and updated to reflect these changes.

## c. ✓ Colloidal Silicon Dioxide:

The testing protocol presented on page 433 reflects the revisions presented in the USP 23's 6th supplement; however, the results, which post-date the protocol, do not reflect the revisions presented in the 6th Supplement.

## d. ✓ Purified Water

The testing protocol presented on page 481 reflects the revisions presented in the USP 23's 5th supplement. The firm should revise the tests and specifications to conform with USP 23, 8th supplement, which becomes official May 15, 1998.

## 2. Controls for the Finished Dosage Form:

a. The Finished Product Specifications include a Specification limit for \_\_\_\_\_  
The identity of this material is not included in the Finished product or Stability sections but is found in the Methods Validation section where it is identified as \_\_\_\_\_

b. The proposed specification limits for single and total impurities of \_\_\_\_\_ %  
\_\_\_\_\_ % in the drug product, respectively, appear to bear little relation to the values found, the maximum value in each case being \_\_\_\_\_ %.

3. The proposed Stability Specifications for single and total impurities of \_\_\_\_\_ % and \_\_\_\_\_ %, respectively, bear little relation to the values found, the maximum value in each case being \_\_\_\_\_ %.

4. The quantity Q specified in the dissolution testing methodology is \_\_\_\_\_ % vs. \_\_\_\_\_ % specified by the innovator. Other differences in this methodology were noted in the review by the Division of Bioequivalence and communicated to the firm in a letter dated 3/13/98. The firm should perform the dissolution testing by the recommended methodology and resubmit data as appropriate.

As noted above, the Division of Bioequivalence sent a deficiency letter on 3/13/98. The first labelling review completed 9/17/97 found several deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS

- ◆ **CMC review of application: Not Approvable, Major Amendment required.**

19. REVIEWER  
R. C. Adams

DATE COMPLETED  
3/30/98

Redacted 22

pages of trade

secret and/or

confidential

commercial

information

*Chem. Review #1*

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-203                      Applicant:                      Watson Laboratories, Inc.

Drug Product: Propafenone Hydrochloride Tablets, 150 mg,  
225 mg, & 300 mg

The deficiencies presented below represent MAJOR deficiencies.

## A. Deficiencies:

## 1. Raw Material Specifications:

## a. New Drug Substance, Propafenone Hydrochloride:

The Certificate of Analysis supplied by the drug substance supplier on page 394 does not include specification limit values for particle size distribution (specification

## b. Sodium Lauryl Sulfate:

Please revise your testing protocol to conform with USP 23, 7th Supplement deleted, test and specification for Organic Volatile Impurities added).

## c. Colloidal Silicon Dioxide:

Your testing protocol presented on page 433 reflects the revisions presented in USP 23, 6th Supplement, but the testing results do not reflect these revisions. Please revise your test report form to conform with your protocol and USP 23, 6th Supplement.

d. Purified Water

Please revise the tests and specifications to conform with USP 23, 8th supplement, which becomes official May 15, 1998.

2. Controls for the Finished Dosage Form:

a. The proposed specification limits for single and total impurities of % and %, respectively, bear little relation to the values found, the maximum value in each case being %.

b. Please identify (by footnote or otherwise) as : as indicated in the Methods Validation section.

3. The proposed Stability Specifications for single and total impurities of % and %, respectively, bear little relation to the values found, the maximum value in each case being %.

4. The dissolution data submitted as part of the Specifications and Testing of the Finished Dosage Form should be obtained as per the recommended procedure in the March 11, 1998 deficiency letter from the Division of Bioequivalence and resubmitted. Your Dissolution Specifications should also be revised to reflect these changes (Q value). }

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Bioequivalence of the drug product has not been established. Please refer to the comments dated March 13, 1998, provided to you via facsimile from our Division of Bioequivalence.

2. All facilities involved in the manufacture of the product must be in compliance with current good manufacturing (cGMP) regulations before the application may be approved.

Sincerely yours,

1 ^

/S/

L1

8/18/98

Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 75-203

3. NAME AND ADDRESS OF APPLICANT

Headquarters:

Watson Laboratories, Inc.  
 311 Bonnie Circle  
 Corona, CA 91720

Manufacturing Facility:

132 Business Center Drive:  
 Manufacturing, Packaging, and Final dosage formulation.  
 311 Bonnie circle:  
 Research and Development, Analytical and stability testing.

4. LEGAL BASIS for ANDA SUBMISSION

Patent exclusivity has expired - see p.15 of application.

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

Propafenone Hydrochloride

7. NONPROPRIETARY NAME

Propafenone Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

Original submission	9/11/97
Corrections: response to telecon	9/26/97
Amendment (bio)	4/29/98
New Correspondence	6/15/98
Amendment (chem)	10/16/98

FDA:

Div. of Bio. Letter	8/18/97
Telephone call re: "loose ends."	9/26/97
Letter of acknowledgment	10/17/97
Labelling review #1 - deficient	11/3/97

Div. of Bio. review and facsimile letter - deficient 3/13/98  
 Chemistry Review No. 1 3/30/98

Chemistry Deficiency letter 8/19/98  
 Bio letter (incomplete) 8/19/98  
 Labeling review (unacceptable) 3/5/99

10. PHARMACOLOGICAL CATEGORY  
 Antiarrhythmic

11. HOW DISPENSED  
 Tablets

12. RELATED IND/NDA/DMF(s)

<u>Number</u>	<u>DMF #</u>	<u>Firm Name</u>	<u>Function</u>
1.*			NDS supplier
2.			HDPE bottles
3.			Colorant
4.			HDPE bottles
5.			HDPE bottles
6.			Resin colorant/bottles
7.			CR caps
8.			Caps resin
9.			Caps resin colorant
10.			Liners and liner seals
11.			Coils

\*DMF Hydrochloride is The DMF for Propafenone

13. DOSAGE FORM  
 Tablets

14. POTENCY  
 150 mg , 225 mg and 300 mg

15. CHEMICAL NAME AND STRUCTURE

C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>.HCl MW = 377.91  
 1-Propanone, 1-[2-[2-hydroxy-3-(propylamino)-propoxy]phenyl]-, hydrochloride  
 2'-[2-Hydroxy-3-(propylamino)propoxy]-3-phenylpropiophenone hydrochloride  
 [34183-22-7]

16. RECORDS AND REPORTS  
 N/A

**17. COMMENTS**

This application for the first generic form of propafenone hydrochloride is well assembled and follows the recommended format.

Propafenone is an antiarrhythmic drug of the general class of  $\beta$ -adrenergic antagonists. Specifically, propafenone is a  $\text{Na}^+$  channel blocking agent that is also a  $\beta$ -adrenergic receptor antagonist. It was the subject of a 1971 German patent and currently is marketed by Knoll Pharmaceutical as Rythmol. This submission is the first generic propafenone application.

**The Division of Bioequivalence letter dated August 19, 1998, states that the application remains incomplete pending the submission of an acceptable fasting study on the 225 mg strength of the Propafenone HCl product. Also, the firm was requested to incorporate the following dissolution test/specification: 900 mL of 0.1N HCl at 37 degrees C using USP 23 apparatus II (paddle) at 75 rpm, NLT % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.**

**DMF's**

DMF's authorized in this submission are eleven in number, ten packaging DMF's and one for the drug substance supplied by . . . . . The application contains all the relevant tests, specifications, and procedures for the ten packaging DMF's. The DMF for drug substance, reviewed for the first time, was submitted in April, 1995, and updated October 21, 1997. Aside from lacking a list of authorized firms, the DMF is in good shape and contains all requisite information.

**Process****Exhibit and Production Batch Sizes, Stability**

For the exhibit batches one granulation batch of 75 kg was used for both the 150 mg and 225 mg strengths and one granulation batch of . . . . . kg for the 300 mg strength. Nominal batch sizes of . . . . . were prepared for, respectively, the 150, 225, and 300 mg tablets, with actual yields somewhat lower. Intended production batch sizes are . . . . . mg tablets, . . . . . mg tablets, and . . . . . mg tablets.

Propafenone hydrochloride drug substance is a remarkably stable compound to acidic and alkaline hydrolyses, and thermal, oxidative, and irradiative conditions. The studies reported in the drug substance DMF and also in the Methods Validation section of this application indicated strongly alkaline hydrolytic and oxidative conditions to be the only studies which resulted in any appreciable degradation. Stability data in the drug substance DMF included 9 months of accelerated stability data and 5 years of long-term data had been collected with no observable degradation.

#### Innovator Specifications:

Jim Short, the reviewer responsible for NDA \_\_\_\_\_ Knoll Pharmaceuticals Rythmol®, supplied the innovator specifications for both the NDS and drug product. See **Table 2A** on page 10 for a comparison of innovator specifications for the NDS with Watson proposed specifications and **Table 6A** on page 21 for a similar comparison for the **Finished Dosage Form**.

**The drug substance and finished drug products proposed impurity specifications were revised per our request. The Finished Dosage Form dissolution parameters were revised to concur with a Division of Bioequivalence recommendation. See appropriate sections for revised specifications.**

#### Deficiencies

The following minor deficiencies were conveyed to the applicant. Responses can be found bolded under each issue.

1. Raw Material Specifications:

- a. New Drug Substance, Propafenone Hydrochloride:  
The COA supplied by the drug substance supplier \_\_\_\_\_ on page 394 does not include specification limits for particle size distribution (test

\_\_\_\_\_ has established a particle size distribution specification for micronized propafenone hydrochloride as NLT % LT microns (page 6, 10/16/98).

- b. Sodium Lauryl Sulfate:  
USP 23's 7th supplement deletes the \_\_\_\_\_ measurement and specification and adds a test and specification for OVI's. The firm's protocol should be revised and updated to reflect these changes.

**The specifications and quality assurance report for sodium lauryl**

sulfate have been updated to reflect our request to add OVI's testing (page 7).

- c. Colloidal Silicon Dioxide:  
The testing protocol presented on page 433 reflects the revisions presented in the USP 23's 6th supplement; however, the results, which post-date the protocol, do not reflect the revisions presented in the 6th Supplement.

**A recent COA for colloidal silicon dioxide in compliance with current USP 23, 6th supplement testing is included and found to conform (page 11).**

- d. Purified Water  
The testing protocol presented on page 481 reflects the revisions presented in the USP 23's 5th supplement. The firm should revise the tests and specifications to conform with USP 23, 8th supplement, which becomes official May 15, 1998.

**The purified water testing protocol is revised to reflect USP 23, supplement 8<sup>th</sup>. Updated specifications are included (page 15).**

2. Controls for the Finished Dosage Form:

- a. The Finished Product Specifications include a Specification limit for  
The identity of this material is not included in the Finished product or Stability sections but is found in the Methods Validation section where it is identified as
- b. The proposed specification limits for single and total impurities of %  
%in the drug product, respectively, appear to bear little relation to the values found, the maximum value in each case being %.

**See Finished Dosage Form Tests/Specifications under item 28, table 6a.**

3. The proposed Stability Specifications for single and total impurities of %  
%, respectively, bear little relation to the values found, the maximum value in each case being %.

See Finished Dosage Form Tests/Specifications under item 28, table 8.

4. The quantity Q specified in the dissolution testing methodology is % specified by the innovator. Other differences in this methodology were noted in the review by the Division of Bioequivalence and communicated to the firm in a letter dated 3/13/98. The firm has revised their proposed dissolution test to be in accordance with the Division of Bioequivalence recommendations conveyed in a letter dated 3/13/98.

18. CONCLUSIONS AND RECOMMENDATIONS

**Recommend not approvable letter to issue conveying the firm the Division of Bioequivalence recommendation to submit data from a bio study conducted on the 225 mg dosage form.**

19. REVIEWER  
Edwin Ramos

DATE COMPLETED  
April 30, 1999

20. COMPONENTS, COMPOSITION

Table 1 next page---Acceptable, see chemist review #1

Redacted 21

pages of trade

secret and/or

confidential

commercial

information

Chem Review #2

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 75-203

3. NAME AND ADDRESS OF APPLICANT

Headquarters:

Watson Laboratories, Inc.  
311 Bonnie Circle  
Corona, CA 91720

Manufacturing Facility:

132 Business Center Drive:  
Manufacturing, Packaging, and Final dosage formulation.  
311 Bonnie circle:  
Research and Development, Analytical and stability testing.

4. LEGAL BASIS for ANDA SUBMISSION

Patent exclusivity has expired - see p.15 of application.

5. SUPPLEMENT(s)

N/A

6. NAME OF DRUG

Propafenone Hydrochloride

7. NONPROPRIETARY NAME

Propafenone Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

Original submission	9/11/97
Corrections: response to telecon	9/26/97
Amendment (bio)	4/29/98
New Correspondence	6/15/98
Amendment (chem)	10/16/98
Bio Amendment	3/16/99
Labeling Amendment	6/16/99
Labeling Amendment	7/16/99
Bio Amendment	3/14/00
Amendment (No CMC changes reported)	6/12/00

FDA:

Div. of Bio. Letter	8/18/97
Telephone call re: "loose ends."	9/26/97
Letter of acknowledgment	10/17/97
Labelling review #1 - deficient	11/3/97
Div. of Bio. review and facsimile letter - deficient	3/13/98

Chemistry Review No. 1	3/30/98
Chemistry Deficiency letter	8/19/98
Bio letter (incomplete)	8/19/98
Labeling review (unacceptable)	3/5/99
Bio review (adequate)	5/4/99
Labeling review (adequate)	6/29/99
NA Letter	8/2/99
Bio NA letter	3/21/00
MV adequate	4/28/00

10. PHARMACOLOGICAL CATEGORY  
Antiarrhythmic

11. HOW DISPENSED  
Tablets

12. RELATED IND/NDA/DMF(s)

<u>DMF #</u>	<u>Firm Name</u>	<u>Function</u>
		NDS supplier
		HDPE bottles
		Colorant
		HDPE bottles
		HDPE bottles
		Resin colorant/bottles
		CR caps
		Caps resin
		Caps resin colorant
		Liners and liner seals
		Coils

\*DMF  
Hydrochloride is

DMF. The

DMF for Propafenone

13. DOSAGE FORM  
Tablets

14. POTENCY  
150 mg and 225 mg

15. CHEMICAL NAME AND STRUCTURE

C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>.HCl MW = 377.91  
1-Propanone, 1-[2-[2-hydroxy-3-(propylamino)-propoxy]phenyl]-, hydrochloride  
2'-[2-Hydroxy-3-(propylamino)propoxy]-3-phenylpropiofenone hydrochloride  
[34183-22-7]

16. RECORDS AND REPORTS  
N/A

17. COMMENTS

Propafenone is an antiarrhythmic drug of the general class of  adrenergic antagonists. Specifically, propafenone is a Na<sup>+</sup>

---

channel blocking agent that is also a B-adrenergic receptor antagonist. It was the subject of a 1971 German patent and currently is marketed by Knoll Pharmaceutical as Rythmol.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approvable letter to issue. The Division of Bioequivalence has found the bio study conducted on the 225-mg dosage form to be acceptable. The firm has withdrawn the 300-mg strength from this application. Any reference to the 300mg strength is not applicable to this review.

19. REVIEWER

Edwin Ramos

DATE COMPLETED

June 22, 2000

Redacted 16

pages of trade

secret and/or

confidential

commercial

information

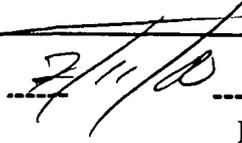
Chem. Review #3

Edwin Ramos

Reviewer

 /S/

Signature



Date