CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-123

CHEMISTRY REVIEW(S)

HFD 550
KONG

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
HFD-550/830
Review of Chemistry, Manufacturing, and Controls

APR 12 2000

NDA #: 21-123 **DATE REVIEWED:** 04/07/00 **Primary Goal**: 7/1/00
REVIEW # 1 **REVIEWER:** Bart Ho

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-aug-99	01-Sep-99	10-Sep-99
Amendments	13-Sep-99, submitting the electronic review aid supporting NDA 21-123		

NAME & ADDRESS OF APPLICANT:
The R.W.Johnson Pharmaceutical Research Institute
920 Route 202 South, P. O. Box 300, Raritan, NJ 08869-0602

DRUG PRODUCT NAME
Proprietary: Ultracet
Established: Tramadol Hydrochloride/Acetaminophen
Code Name/#:
Chem.Type/Ther.Class:

REMARKS:

Drug Substance:

Tramadol Hydrochloride:

Information on tramadol HCl is provided in NDA 20-281. The drug substance will be supplied by [redacted] The use of tramadol HCl from these two suppliers was regarded as qualified. Reference to review information provided in NDA-20-281 was provided.

Acetaminophen:

Information on acetaminophen was provided in DMF [redacted] Acetaminophen will be supplied by [redacted] The drug master file was reviewed and was found satisfactory.

Drug Product:

Information on the formulation of the drug product, manufacturing process, in-process control, tests and specifications, container/closure systems and satisfactory 24 months stability data on three production batches of the drug product are all provided. However, the NDA contains CMC deficiencies that need to be addressed. See Chemist's Review Notes for details. The overall recommendation from the Office of Compliance is still pending.

CONCLUSIONS & RECOMMENDATIONS:

From the chemistry stand point, the NDA is approvable contingent upon satisfactory responses to CMC deficiencies and overall acceptable recommendation from the Office of Compliance. Please communicate the deficiencies to the applicant provided at the end of this review.

/S/

Bart Ho, Review Chemist 4/12/00.

/S/

Mona Zarifa, Acting Team Leader 4/12/00

cc:
Org. NDA 21-123
HFD-550/Division File
HFD-550/Pharm. Tox.
HFD-550/Lee
HFD-550/BHo/Zarifa
HFD-550/Kong
HFD-830/Chen

27 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs
HFD-550/830

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-123 **DATE REVIEWED:** 06/05/00 **Primary Goal:** 7/1/00

REVIEW # 2 **REVIEWER:** Bart Ho

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	31-aug-99	01-Sep-99	10-Sep-99
Amendment 1	13-Sep-99, submitting the electronic review aid supporting NDA 21-123		
Amendment 2	7-April-00		
Amendment 3	1-May-00, response to our IR letter (Subject to this review)		

NAME & ADDRESS OF APPLICANT:

The R.W.Johnson Pharmaceutical Research Institute
920 Route 202 South, P. O. Box 300, Raritan, NJ 08869-0602

DRUG PRODUCT NAME

Proprietary: Ultracet
Established: Tramadol Hydrochloride/Acetaminophen
Code Name/#:
Chem.Type/Ther.Class: 4

PHARMACOL. CATEGORY: Management of [redacted] acute [redacted] pain.
DOSAGE FORM: Tablet
STRENGTHS: Tramadol Hydrochloride (37.5 mg)/Acetaminophen (325 mg)
ROUTE OF ADMINISTRATION:
DISPENSED: _X_ Rx ____OTC

REMARKS:

The original CMC submission has been reviewed in review #1and was found deficient. Deficiencies were telefaxed to R. W. Johnson (RWJ) on 3/28/00. In response, RWJ amended the application on 4/7/00 and requested to have a teleconference(telecon) with the Agency to discuss the deficiencies. A telecon was held on 4/11/00 (see attached minutes). The May 1, 2000 amendment is a follow up to provide RWJ's complete response to the CMC deficiencies. Based on the chemistry point of view, NDA 21-123 is complete. See review for details.

CONCLUSIONS & RECOMMENDATIONS:

From the chemistry stand point, the NDA is approvable contingent upon an overall acceptable recommendation from the Office of Compliance.

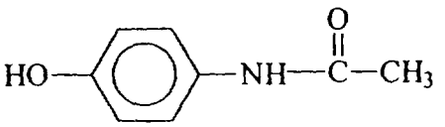
SPECIAL PRODUCTS ____Yes _X_ No
CONSULTS:

BioPharm: A consult was sent to BioPharm in regard to RWJ's proposed dissolution specification. BioPharm agrees with RWJ's revised specification.

Method Validation:
Method validation package has been sent to Philadelphia District Office.
Current status: Pending on the result of the validation

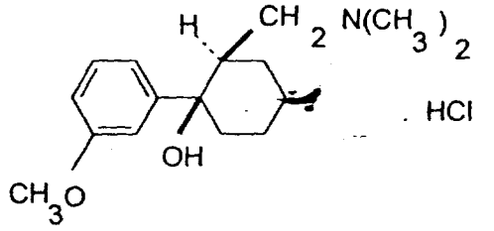
EER: An EER requesting to conduct inspection of the facilities provided in the application was sent to the Compliance. Recommendation from the Office of Compliance remains to be pending.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



Acetaminophen, $C_8H_9NO_2$

M. W. = 151.17



TRAMADOL . HCl

M. W. = 299.84

Formular: $C_{16}H_{25}NO_2$ .HCl

SUPPORTING DOCUMENTS:

NDA 20-281, Tramadol HCl
IND# [redacted]
DMFs: See table below

Type/No.	Subject	Holder	Status	Review Date	LOA
[redacted]			Adequate	8/14/98	10/1/98
			Adequate	NA	9/18/98
			Adequate	NA	9/18/98
			Adequate	NA	9/23/98
			Adequate	2-22-99	
			Adequate	NA	

RELATED DOCUMENTS: NONE

/S/

Bart Ho, Review Chemist

/S/

Mona Zarifa, Acting Team Leader

cc:
Org. NDA 21-123
HFD-550/Division File
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