

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40352

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 40-352

SPONSOR: Mallinckrodt Inc.

DRUG & DOSAGE FORM: Meperidine HCl Tablets

STRENGTH(s): 50 mg

TYPE OF STUDY:

SD

SDF

MULT X OTHER

STUDY SUMMARY: Dissolution is acceptable.
Waiver is granted.

PRIMARY REVIEWER : Jahnvi S. Kharidia

INITIAL : JS

BRANCH : 3

DATE : 2/18/99

Team Leader : Barbara M. Davit

INITIAL : BD

BRANCH : 3

DATE : 2/18/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : SM

DATE : 2/19/99

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____

DATE : _____

(6)

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 40-352

SPONSOR : Mallinckrodt Inc.

DRUG AND DOSAGE FORM : Meperidine Hydrochloride Tablets

STRENGTH(S) : 100 mg

TYPES OF STUDIES : N/A – Waiver Request

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : N/A

DISSOLUTION : AC

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
NO		
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Jahnvi S. Kharidia, Ph.D. BRANCH : 3

INITIAL : JS DATE : 4/22/99

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : 3

INITIAL : JS DATE : 4/22/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DP DATE : 4/27/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-352

APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Meperidine Hydrochloride Tablets, 100 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours. ↗

Dale P. Conner, Pharm. D. ↗
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Meperidine Hydrochloride
 100 mg Tablets
 ANDA # 40-352
 Reviewer: Jahnvi S. Kharidia

Mallinckrodt Inc.
 675 McDonnell Blvd
 St. Louis, MO 63134
 Submission Date:
 March 22, 1999

Review of an Amendment

Objective:

The firm's application for 50 mg meperidine tablet was found acceptable by the DBE (Review Date: February 19, 1999). The firm is now submitting this amendment for an additional strength, 100 mg meperidine tablet. The firm is requesting a waiver of the bioequivalence requirement for their meperidine hydrochloride tablets, 100 mg under 21 CFR Section 320.22(C). The RLD is Demerol® tablets, 100 mg, by Winthrop Pharmaceuticals.

Formulation:

Ingredient	50 mg Tablet (mg/Tablet)	100 mg Tablet (mg/Tablet)
✓ Meperidine HCl USP	50.0	100
✓ Dibasic Calcium Phosphate USP (Emcompress)		
✓ Magnesium Stearate NF		
✓ Microcrystalline Cellulose NF (Avicel PH 101)		
✓ Povidone USP		
✓ Pregelatinized Starch NF		
✓ Stearic Acid NF		
✓ Talc USP		
Total Weight		

Dissolution:

The comparative dissolution data are summarized below:

<i>In Vitro</i> Dissolution Testing						
Drug (Generic Name): Meperidine Hydrochloride						
Dosage Form: Tablets						
Dose Strength: 50 mg -						
I. Conditions for Dissolution Testing:						
Apparatus: Basket, I Speed: 100 RPM No. Units: 12 Tablets Medium: water			Volume: 500 mL Sampling Time: 15, 30, 45 and 60 minutes Specification: NLT % (Q) in 45 minutes			
II. Results of In Vitro Dissolution Testing: 50 mg Tablet						
Time	Test Product # Lot # MHSC 9836			Reference Product * Lot # SH 393		
	Mean	Range	% RSD	Mean	Range	% RSD
15	101.4		2.7	100.5		3.6
30	100.3		1.5	99.0		2.3
45	98.0		1.7	96.1		1.8
60	96.0		2.0	93.5		2.1

III. Results of In Vitro Dissolution Testing: 100 mg Tablet						
Time	Test Product			Reference Product		
	Lot # MHSC 9854			Lot # SH 368		
	Mean	Range	% RSD	Mean	Range	% RSD
15	87.8		4.6	87.1		9.4
30	101.9		1.7	95.5		2.9
45	100.6		2.0	94.3		2.0
60	97.5		2.1	91.7		2.1

F2 Value Comparison

Test 50 mg tablets vs. Test 100 mg tablets

* Reference 50 mg tablets vs. Reference 100 mg tablets

Comments:

1. The product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
2. The firm has submitted comparative *in vitro* dissolution data on meperidine hydrochloride tablets (100 mg) and the listed reference product; Demerol[®] tablets (100 mg). The dissolution data are acceptable.
3. The formulation of Mallinckrodt's 100 mg meperidine hydrochloride tablet is proportional to that of the previously approved 50 mg tablet.
4. A waiver for meperidine hydrochloride tablets is granted under 21 CFR Section 320.22 (C) of the Bioavailability / Bioequivalence Regulations.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Mallinckrodt Inc. demonstrates that meperidine hydrochloride 50 mg tablets falls under 21 CFR Section 320.22 (C) of the Bioavailability / Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an *in vivo* bioequivalence study be granted. Mallinckrodt's meperidine hydrochloride 100 mg tablets are deemed bioequivalent to Demerol[®] 100 mg tablets manufactured by Winthrop Pharmaceuticals.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37° C using USP XXIII Apparatus I (basket) at 100 RPM. The test should meet the following specification:

Not less than % (Q) of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

ISI
Jahnavi S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch II

BAS 4/21/99

RD INITIALED BDAVIT
FT INITIALED BDAVIT

ISI Date: 4/22/99

Concur ISI Date: 4/27/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-352

APPLICANT: Mallinckrodt Inc.

DRUG PRODUCT: Meperidine Hydrochloride Tablets, 50 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours.


Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA#: 65-014
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer
HFD-650/T. Leader

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2/18/99

Endorsements: (Final with Dates)

HFD-655/ J. Kharidia 2/18/99

HFD-655/ B. Davit 2/18/99

HFD-650/ D. Conner 2/19/99

BIOEQUIVALENCY - ACCEPTABLE submission date: November 25, 1998

7. Dissolution Waiver (DIW) Strengths: 50 mg
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: Waiver is granted

Meperidine Hydrochloride
 50 mg Tablets
 ANDA # 40-352
 Reviewer: Jahnvi S. Kharidia

Mallinckrodt Inc.
 675 McDonnell Blvd
 St. Louis, MO 63134
 Submission Date:
 December 23, 1998

Review of Dissolution Data and a Waiver Request

Objective:

The firm has requested a waiver of the bioequivalence requirement for their meperidine hydrochloride tablets, 50 mg under 21 CFR Section 320.22 (C). The RLD is Demerol® tablets, 50 mg, by Winthrop Pharmaceuticals.

Formulation:

Ingredient	Quantity (mg/Tablet)
Meperidine HCl USP	50.0
Dibasic Calcium Phosphate USP (Emcompress)	
Magnesium Stearate NF	
Microcrystalline Cellulose NF (Avicel PH 101)	
Povidone USP	
Pregelatinized Starch NF	
Stearic Acid NF	
Talc USP	
Total Weight	

Dissolution:

The comparative dissolution data are summarized below:

<i>In Vitro</i> Dissolution Testing						
Drug (Generic Name): Meperidine Hydrochloride						
Dosage Form: Tablets						
Dose Strength: 50 mg						
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Comments:

1. The product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".
2. The firm has submitted comparative *in vitro* dissolution data on meperidine hydrochloride tablets (50 mg) and the listed reference product, Demerol® tablets (50 mg). The dissolution data are acceptable.
3. A waiver for meperidine hydrochloride tablets is granted under 21 CFR Section 320.22 (C) of the Bioavailability / Bioequivalence Regulations.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Mallinckrodt Inc. demonstrates that meperidine hydrochloride 50 mg tablets falls under 21 CFR Section 320.22 (C) of the Bioavailability / Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an *in vivo* bioequivalence study be granted. Mallinckrodt's meperidine hydrochloride 50 mg tablets are deemed bioequivalent to Demerol® 50 mg tablets manufactured by Winthrop Pharmaceuticals.
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/S/

Jahnvi S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch II

2/18/99

RD INITIALED BDAVIT
FT INITIALED BDAVIT

/S/ Date: *2/18/99*

Concur

/S/

Date: *2/19/99*

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence