CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-073/S013

Trade Name: Actos Tablets

Generic Name: pioglitazone HCL

Sponsor: Takeda Pharmaceuticals North America, Inc.

Approval Date: October 1, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-073/S013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S013

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-073/S-013

Takeda Pharmaceuticals North America, Inc.
Attention: Robert J. Pilson, R.Ph., J.D.
Manager, Regulatory Compliance
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Dr. Pilson:

Please refer to your supplemental new drug applications dated May 9, 2001, received May 11, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) tablets, 15 mg, 30 mg and 45 mg.

We acknowledge receipt of your submissions dated October 9, 2001, and February 1, and May 30, 2002.

Your submission of May 30, 2002, constituted a complete response to our July 29, 2001, action letter.

This supplemental new drug application provides for a modification of the dissolution method for Actos®(pioglitazone HCl) from a "Q" value of [redacted] in 30 minutes at 50 RPM's, to a "Q" value of [redacted] in 15 minutes at 75 RPM's.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drugs Evaluation and Research

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/s/

David Orloff
10/1/02 05:33:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S013

NOT APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-073/S-013

Takeda Pharmaceuticals North America, Inc.
Attention: Linda J. Peters
Director, Regulatory Affairs
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Ms. Peters:

Please refer to your supplemental new drug application dated May 9, 2001, received May 11, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone hydrochloride) tablets, 15 mg, 30, and 45 mg.

We acknowledge receipt of your submission dated May 24, 2001, containing the validation report for the revision of the dissolution method.

This supplement proposes a revised dissolution change to increase the paddle speed from 50 RPM to 75 RPM.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The Agency recommends that the dissolution method and specifications for Actos® remain unchanged. Dissolution specifications are generally set so that products can routinely pass USP stage 1 testing. However, if a portion of the product line (———————) is occasionally forced to proceed to USP Stage 2 testing, it does not mean that the dissolution method and tolerance specifications are inappropriate and need to be changed.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S013

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

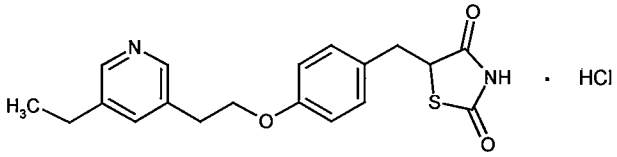
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 21-073** Approved: 21-JUL-1999
Name and Address of Applicant: Takeda Pharmaceuticals America Inc. 101 Carnegie Center, Suite 207 Princeton, NJ 08540 Phone: (609) 452-1113 x-4409 Fax: (609) 452-1218	**Supplement** SCS-013 Doc. 09-MAY-2001 Rec. 11-MAY-2001 **Name Of The Drug** Actos™ Tablets **Nonproprietary Name** Pioglitazone Hydrochloride Tablets
Supplement provides a revised Dissolution method. In particular it is proposed to increase the paddle speed, currently at 50 rpm, to 75 rpm.	**Amendment(s)** Doc. 24-MAY-2001 Rec. 25-MAY-2001

Pharmacological Category:	**How Dispensed**	**Supporting Documents**
Hypoglycemic Agent, treatment of NIDDM.	Oral Rx	--
Dosage Form Tablets	**Potencies** 15-, 30- and 45-mg	

Chemical Name and Structure

Pioglitazone

$C_{19}H_{20}N_2O_3S \cdot HCl$
MW = 356.43 + 36.57 = 392.90



(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

Comments: This –Prior Approval- Supplement provides for the revision of the Actos® tablets dissolution specification. The current dissolution method uses USP apparatus 2 with a paddle speed of 50 rpm, 900 mL hydrochloric acid buffer pH 2.0, with the specification that ~ (Q) at 30 minutes. The proposed revised dissolution specification would only differ in one test condition, the paddle speed would be increased from 50 rpm to 75 rpm. This request was based after a stability study ( ), carried out by , prompted by the failure of (Lot 45045ZE, with an unusual dissolution result of % in 30 minutes) to meet specifications. As noted by the applicant this result has not been reproducible. Typical dissolution values indicate the more than is dissolved after minutes. Based on the experimental data, the particular outlier dissolution value found in of lot 45045ZE is considered a rarity that does not merit the change in dissolution conditions. This supplemental application was also evaluated by the Biopharm Division (see Dr. Stephen Johnson review dated 10-JUL-2001). Based on Dr. Johnson's review, who requested additional information (amendment 24-MAY-2001), the Office of Clinical Pharmacology and Biopharmaceutics recommends that dissolution method for Actos ® Tablets remain unchanged. *We concur with Biopharm's recommendation.*

Conclusions and Recommendations: Based on the Biopharm review and recommendation, it is deemed that the dissolution specification should remain unchanged. From the chemistry point of view, this supplement cannot be approved. **Issue non-approval letter.**

Reviewer Name (and signature) **Date Completed:** 13-JUL-2001

Xavier Ysern, PhD

R/D Init.

filename: /nda/21073s13.doc

DISTRIBUTION: Original: NDA 21-073 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

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/s/

Xavier Ysern
7/19/01 05:13:58 PM
CHEMIST

NA

Stephen Moore
7/20/01 11:12:27 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-073/S013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-073 / SCS-013		
BRAND NAME:	ACTOS®	**GENERIC NAME:**	Pioglitazone hydrochloride
STRENGTH(S):	15 mg, 30 mg, and 45 mg tablets		
SPONSOR:	Takeda Pharmaceuticals North America, Inc 475 Half Day Road – Suite 500, Lincolnshire, IL 60069		
SUBMISSION DATE:	30-MAY-2002	**PDUFA DATE:**	30-SEP-2002
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

SYNOPSIS

On May 9, 2001, Takeda Pharmaceuticals North America submitted a supplement requesting that a revision be made to their currently approved ACTOS® dissolution method (Table 1) with a nearly identical method (Table 2). The sponsor has requested this change because the approved method was found to be too sensitive to small variations in tablet position in the dissolution vessel and to slight increases in paddle height .

Table 1: Approved Dissolution Method and Tolerance Specifications – pioglitazone hydrochloride	
Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	**50 RPM**
Tolerance	NLT (Q) @ 30 minutes

Table 2: Proposed Dissolution Method and Tolerance Specifications – pioglitazone hydrochloride	
Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	**75 RPM**
Tolerance	NLT (Q) @ / minutes

After having reviewed that document, the Office of Clinical Pharmacology and Biopharmaceutics provided the clinical division with the following recommendation and a letter to the sponsor was issued on July 29, 2001, that stated the following:

"The Office of Clinical Pharmacology and Biopharmaceutics recommends that the dissolution method and specifications for ACTOS® (pioglitazone hydrochloride) remain unchanged. The Agency does not typically set dissolution specifications based on the dissolution results of a tablet. The mere requirement of certain strength in a product line occasionally proceed to USP Stage 2 testing is not a compelling argument to suggest that the dissolution method and tolerance specifications are inappropriate."

On February 8, 2002, a teleconference was held between the Division and representatives from Takeda. At that time, Dr. Hae-Young Ahn requested that Takeda submit additional dissolution data on lots each for ACTOS 15, 30, and 45 mg strength tablets tested at 50 and 75 RPM. Results of the new data suggest that the original tolerance specifications were perhaps too rigid for ACTOS tablets. This change is qualified by the fact that when the original tolerance specifications and paddle speed were employed, the results were not reproducible. The reason that the results were not reproducible is likely due to the coning issue that is associated with the use of a paddle speed of 50 RPM. Therefore, a modification of the dissolution method for ACTOS, from (Q) @ 30 minutes using a paddle speed of 50 RPM to (Q) @ 15 minutes using a paddle speed of 75 RPM , is warranted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-073 supplement 13 and recommends that the dissolution method and specifications for ACTOS® (pioglitazone hydrochloride) be changed as follows:

Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	**75 RPM**
Tolerance	**NLT (Q) @ 15 minutes**

DISSOLUTION

– Effect of Paddle Rotation Speed –

15 mg Tablets

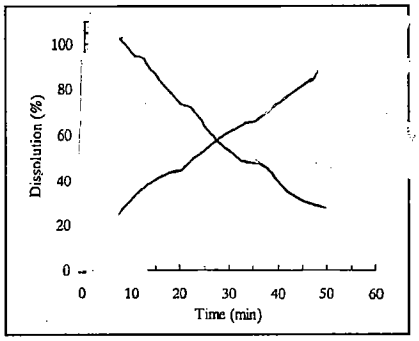


Table 1-1 Effect of the paddle rotation speeds (15mg tablets, Lot No. Z509P01)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1	Min.	0					
		Max.	0					
		Average	0					
	2	Min.	0					
		Max.	0					
		Average	0					
	3	Min.	0					
		Max.	0					
		Average	0					
	Total	Average	0					
		S.D.	-					
75rpm	1	Min.	0					
		Max.	0					
		Average	0					
	2	Min.	0					
		Max.	0					
		Average	0					
	3	Min.	0					
		Max.	0					
		Average	0					
	Total	Average	0					
		S.D.	-	1.8	1.4	1.4	1.3	1.4

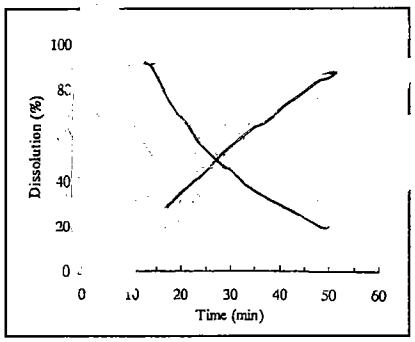


Table 1-2 Effect of the paddle rotation speeds (15mg tablets, Lot No. O-064)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.						
75rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.	-	1.4	1.3	1.2	1.2	1.2

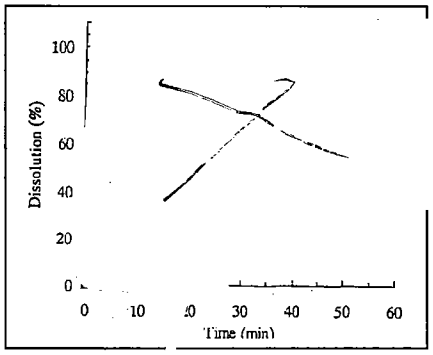


Table 1-3 Effect of the paddle rotation speeds (15mg tablets, Lot No. O-065)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1							
	2							
	3							
	Total							
75rpm	1							
	2							
	3							
	Total							

30 mg Tablets

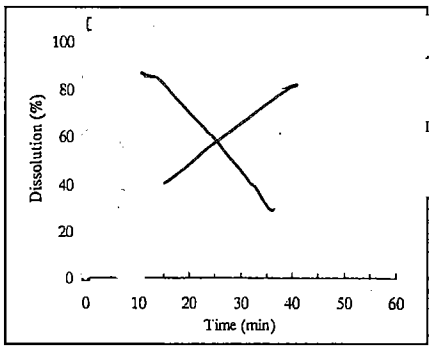


Table 2-1 Effect of the paddle rotation speeds (30mg tablets, Lot No. Z509I12)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1							
	2							
	3							
	Total							
75rpm	1							
	2							
	3							
	Total							

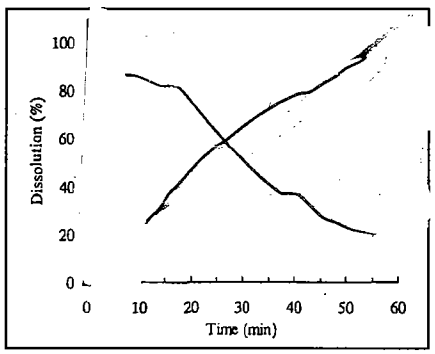


Table 2-2 Effect of the paddle rotation speeds (30mg tablets, Lot No. O-101)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1							
	2							
	3							
	Total							
75rpm	1							
	2							
	3							
	Total							

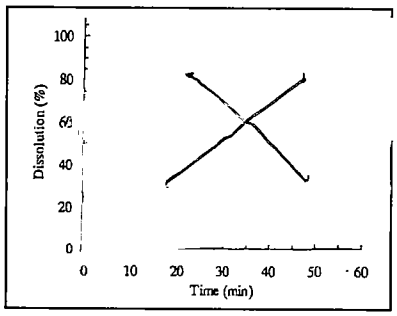


Table 2-3 Effect of the paddle rotation speeds (30mg tablets, Lot No. O-102)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1							
	2							
	3							
	Total							
75rpm	1							
	2							
	3							
	Total							

45 mg Tablets

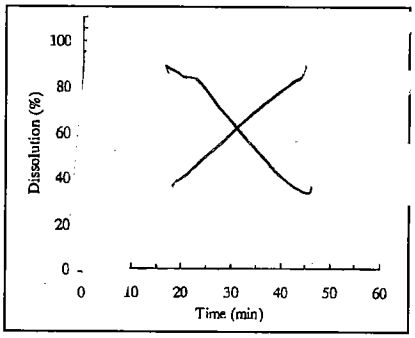


Table 3-1 Effect of the paddle rotation speeds (45mg tablets, Lot No. Z509N01)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.						
75rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.						

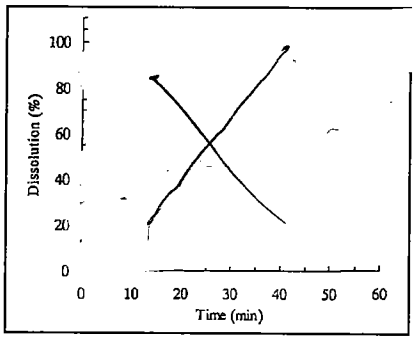


Table 3-2 Effect of the paddle rotation speeds (45mg tablets, Lot No. O-099)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1							
	2							
	3							
	Total							
75rpm	1							
	2							
	3							
	Total							

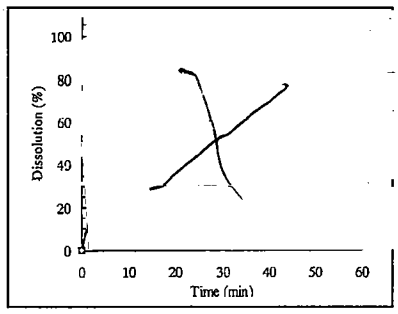
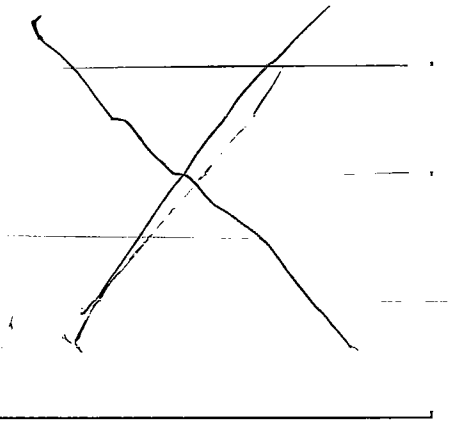


Table 3-3 Effect of the paddle rotation speeds (45mg tablets, Lot No. O-100)

Paddle speed	Repeat	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.						
75rpm	1	Min.						
		Max.						
		Average						
	2	Min.						
		Max.						
		Average						
	3	Min.						
		Max.						
		Average						
	Total	Average						
		S.D.						



Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader: 30-SEP-2002

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/s/

Steve Johnson
9/30/02 04:38:39 PM
BIOPHARMACEUTICS

Hae-Young Ahn
9/30/02 04:44:36 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-073 / SCS-013		
BRAND NAME:	ACTOS®	**GENERIC NAME:**	Pioglitazone hydrochloride
STRENGTH(S):	15 mg, 30 mg, and 45 mg tablets		
SPONSOR:	Takeda Pharmaceuticals North America, Inc 475 Half Day Road – Suite 500, Lincolnshire, IL 60069		
SUBMISSION DATE:	9-MAY-2001	**REVIEW DATE:**	2-JUL-2001
CPB REVIEWER:	Steven B. Johnson, Pharm.D.		
CPB TEAM LEADER:	Hae-Young Ahn, Ph.D.		

SYNOPSIS

Takeda Pharmaceuticals North America has submitted a supplement requesting revision to their currently approved ACTOS® dissolution method (Table 1) with a nearly identical method (Table 2) that increases the paddle speed from 50 RPM to 75 RPM. The sponsor has requested this change because the approved method was found to be too sensitive to small variations in tablet positior ——— in the dissolution vessel and to slight increases in paddle height —

Table 1: Approved Dissolution Method and Tolerance Specifications – pioglitazone hydrochloride

Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	**50 RPM**
Tolerance	NLT — ,Q) @ 30 minutes

Table 2: Proposed Dissolution Method and Tolerance Specifications – pioglitazone hydrochloride

Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	**75 RPM**
Tolerance	NLT — Q) @ / minutes

Included in this supplement are an investigation of the effect of paddle speed, tablet position, and paddle height on ACTOS® dissolution rates and a study that evaluates the discriminatory power of the proposed method.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics recommends that the dissolution method and specifications for ACTOS® (pioglitazone hydrochloride) remain unchanged. The Agency does not typically set dissolution specifications based on the dissolution results of a ——— The mere requirement of a certain strength in a product line ——— to occasionally proceed to USP Stage 2 testing is not a compelling argument to suggest that the dissolution method and tolerance specifications are inappropriate.

DISSOLUTION

– Effect of Paddle Speed –

The sponsor's primary concern with the original method at 50 RPM was that unpredictable coning occurred resulting in slower dissolution rates at the 30 minute time point which often necessitated USP Stage 2 testing. As such, paddle rotation speeds at 50 RPM, 75 RPM, and 100 RPM were compared for each tablet strength. The major focus was on the switch from the 50 to 75 RPM paddle speed.

15 mg Tablets

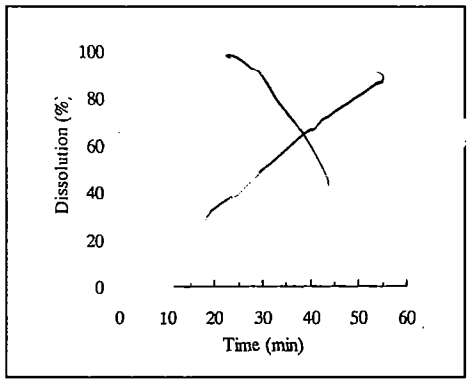

Table 1-1 Effect of the paddle rotation speeds (15mg tablets, Lot No. Z509P01)

Paddle speed	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm							
75rpm							
100rpm							

30 mg Tablets

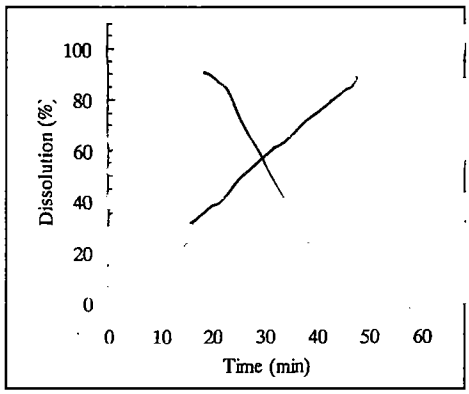

Table 1-2 Effect of the paddle rotation speeds (30mg tablets, Lot No. Z509I12)

Paddle speed	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm							
75rpm							
100rpm							

45 mg Tablets

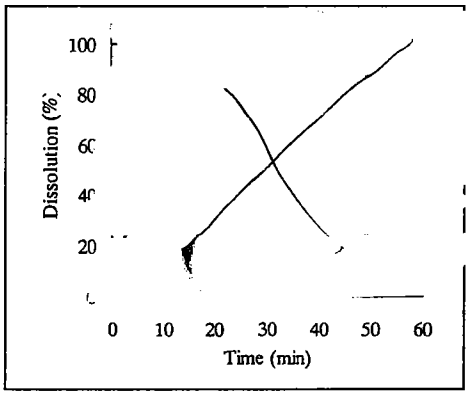

Table 1-3 Effect of the paddle rotation speeds (45mg tablets, Lot No. Z509N01)

Paddle speed	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm							
75rpm							
100rpm							

Results of these studies showed that when the paddle speed was increased from 50 RPM to either 75 RPM or 100 RPM, the standard deviation was substantially reduced and the amount of pioglitazone dissolved increased

Note: Dissolution specifications are generally set so that products can routinely pass USP Stage 1 testing. However, if a portion of the product line is occasionally forced to proceed to USP Stage 2 testing, this does not mean that the method and specifications are flawed and need to be changed.

– Effect of Tablet Position –

In order to evaluate the effect of tablet position in the dissolution vessel, the sponsor conducted dissolution studies in which the tablet was either placed in the [redacted] of the vessel. Paddle speeds of 50 RPM and 75 RPM were used in this comparison.

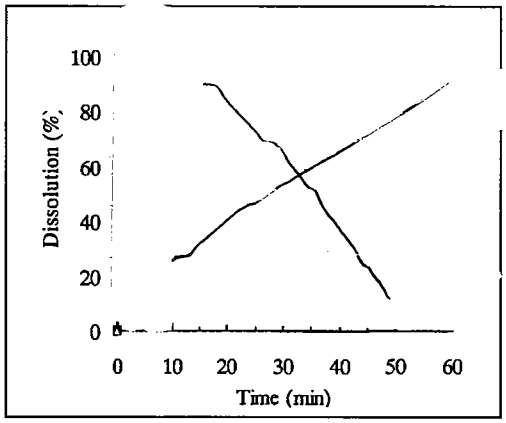

Table 2 Effect of the tablet position

Paddle speed	Tablet position	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm								
	[redacted]							
75rpm								
	[redacted]							

Results of this study are inconclusive for an obvious reason: the sponsor did not compare [redacted] for the 50 RPM paddle speed. Without this information it is not clear whether the similarity of the two profiles seen at 75 RPM is due to the tablet placement or just the result of the increased paddle speed. In addition, the profiles that are presented for the 50 RPM [redacted] placement appear to be very similar to those presented in other dissolution studies. This would suggest that the "effect of tablet position" in the vessel has a marginal effect, at best, for this product.

– Effect of Paddle Height –

To determine the effect of paddle height on the dissolution rate of ACTOS®, the sponsor has conducted a study that compared paddle heights of [redacted] and [redacted] at 50 and 75 RPM.

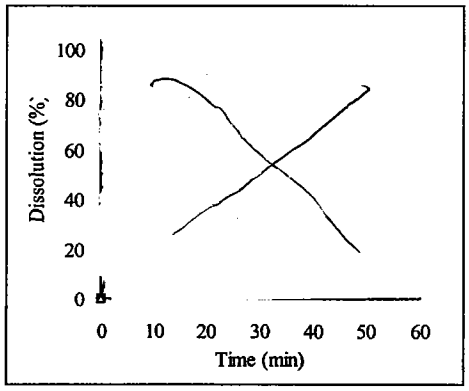

Table 3 Effect of the paddle height

Paddle speed	Paddle height	Calculation	Dissolution rate (%) 0	10	20	30	45	60
50rpm								
	[redacted]							
75rpm								
	[redacted]							

Results of this study showed that at 75 RPM, paddle height had no influence on ACTOS® dissolution. Although not included in this study, it appears that the dissolution rate at 50 RPM is reduced when the paddle height [redacted]

– Discriminatory Power –

The discriminatory power of the dissolution method at 75 RPM was evaluated by comparing a commercial batch manufactured by the approved method with [redacted] Results are presented in the following strength specific plots and tables:

15 mg Tablets

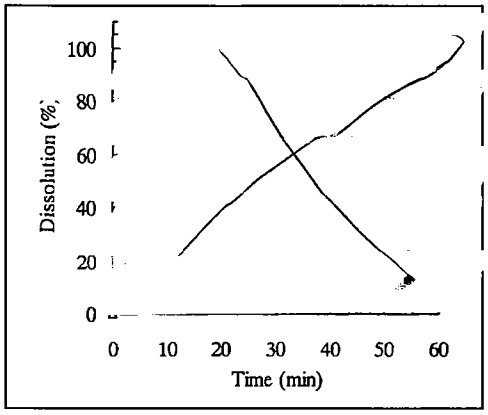

Table 4-1 Dissolution data for ACTOS 15mg

Lot No.	Calculation	Dissolution rate (%) 0	10	20	30	45	60

30 mg Tablets

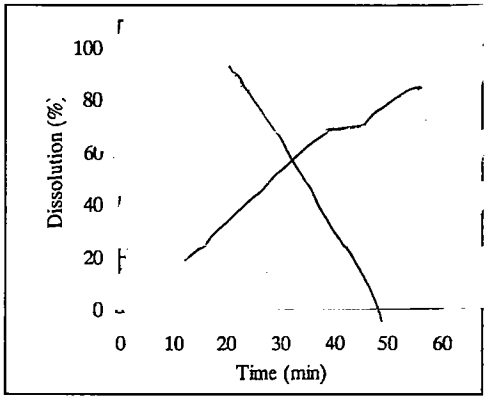

Table 4-2 Dissolution data of ACTOS 30mg tablets

Lot No.	Calculation	Dissolution rate (%) 0	10	20	30	45	60

45 mg Tablets

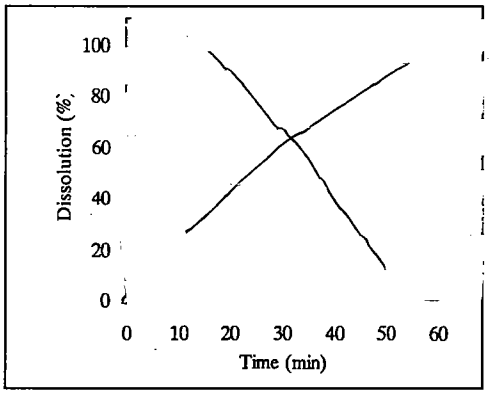

Table 4-3 Dissolution data of ACTOS 45mg tablets

Lot No.	Calculation	Dissolution rate (%) 0	10	20	30	45	60

Results clearly show a demonstrable difference between the tablets produced by the approved method (commercial) [redacted] However, the relevancy of comparing these two methods to demonstrate "discriminatory power" is flawed. The real question that should be asked is, "do these two different manufacturing methods lead to different ACTOS® pharmacokinetic profiles and bioavailability?" Without this information, a comparison of this sort seems to be misleading.

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 10-JUL-2001
FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 10-JUL-2001

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/s/

Steve Johnson
7/20/01 09:16:14 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/8/01 09:30:59 AM
BIOPHARMACEUTICS

MEMORANDUM OF TELECON

DATE: Friday February 8, 2002; 10 am.

APPLICATION NUMBER: NDA 21-073/S-013 Actos (pioglitazone) Tablets

BETWEEN:

FDA participants:

Hae-Young Ahn, Ph.D.	Team Leader, Biopharmaceutics
Steven Johnson, PharmD	Biopharmaceutics Reviewer
Kati Johnson, R.Ph.	Supervisor Project Management Staff
Jena Weber, BS	Project Manager

Takeda Pharmaceuticals North America, Inc.

James Morley, Ph.D.	CMC
Jeff Soderquist, MBA	CMC
Robert Pilson, J.D.	Regulatory Affairs
Chris Rojewski, BS	CMC

SUBJECT: Dissolution specifications (methods) for Actos Tablets.

Supplement - 013 was submitted on May 9, 2001, requesting that revisions be made to the current dissolution method. FDA responded with a **not approvable** letter on July 29, 2001. Takeda provided an amendment to S-013, on February 1, 2002, requesting a t-con to discuss changing the dissolution specifications for Actos, specifically the tablet.

General Background:

When the NDA was submitted, Takeda proposed that the dissolution tolerances be set at (Q at . However, when this NDA was approved, the Agency set the tolerance specifications to NLT (Q) @ 30 minutes, using a 50 RPM paddle speed. Supplement 013, submitted May 9, 2001, proposed to increase the paddle speed in the dissolution testing to 75 RPM. The company requested this change because of the requirement for some tablets to go to stage 2 (S2) testing.

General Discussion:

The May 9, 2001, amendment to the supplement reported dissolution failure; stating unknown causes, a random occurrence, possibly due to "coning," or test method related.

Coning could result in slower dissolution rates (at 30 minutes), thereby requiring Stage 2 testing, even though the failure was not considered representative of the lot investigated for the [redacted] tablets. The company has not been able to duplicate this result. However, according to Takeda, this event was not entirely unexpected, as the occurrence of Stage 2 (S2) testing is more than occasional.

The May 24, 2001, amendment provided an additional validation report in support to revise the dissolution method. The company offered a possible explanation that the total mass of the [redacted] tablet is [redacted] greater than the [redacted] tablets, and that "coning" does not appear when the paddle speed is at 75 rpm, and the tablet location in the dissolution vessel does not influence the rate of release. Nevertheless, as specified in Dr. Steven Johnson's review of supplement 013, tablet location [redacted], results are not convincing as the company did not compare [redacted] for the 50 rpm paddle speed.

Takeda proposed the following 3 options:

- Change the paddle speed to 75 rpm for all strength tablets.
- [redacted]
- [redacted]

The Agency provided the following response:

1. In the May 24, 2001 submission, the dissolution at 75 rpm and 100 rpm paddle speed is identical. Therefore, the 75 rpm speed is not discriminatory. In addition, information was only provided [redacted] lot for each strength tablet. The dissolution specification can not be revised based on information from [redacted] lot.

2. The Agency does not share the firm's concern that the requirement to go to Stage 2 testing indicates that there is a problem.

Conclusions:

Takeda will provide a **complete response** to our N/A letter that will include multipoint dissolution profile data on [redacted] strength tablet at a paddle speed of 50 and 75 rpm. This additional data will allow the Agency to better estimate if the dissolution tolerance specification for the Actos [redacted] tablets should be changed.

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/s/

Jena Weber
4/11/02 02:51:55 PM
CSO

Hae-Young Ahn
4/15/02 04:08:47 PM
BIOPHARMACEUTICS