Table 4.1
AUC for Healthy Volunteers

Subject	Dose of Lidocaine (ug)	t 1/2 Life	AUC Infusion	AUC Patch Loading 12 Hours	AUC Patch Loading 3 x 12 Hrs	Clearance (L./min.)	Sex	Weight	Age
Healthy Volunteers									
101									
102									
103									
104									
105									
106									
107									
109									
110									
111									
112									
113									
114									
115									
116									
Mean		106.9	49927.4	102725.4	306605.6	0.635			
Std.		22.0	14544.7	49695.5	119259.1	0.175			

SOURCE: KG/HHC\PK/EFF01 (May 23, 1996 12:48)

Table 4.2
Dose Absorbed for Healthy Volunteers

Subject	Dose Absorbed AUC Patch Loading 12 Hours (ug)	Dose Absorbed AUC Patch Loading 3 x 12 Hrs (ug)	Flux AUC Patch Loading 12 Hours (ug/cm2/hr)	Flux AUC Patch Loading 3 x 12 Hrs (ug/cm2/hr)	Sex	Weight	Age
Healthy Volunteers							
101							
102							
103							
104							
105							
106							
107							
109							
110							
111							
112							
113							
114							
115							
116							
Mean	63772.9	188169.6	12.65	12.45			
Std.	32468.9	72249.5	6.44	4.78			

SOURCE: KG/HHC\PK/EFF04 (May 23, 1996 13:26)

904

Table 4.3
Maximum Concentration and Time for Healthy Volunteers

Subject	Patch Loading 12 Hours		Patch Loading 3 x 12 Hours					
			Maximum Concentration			Time (Hours) of Maximum Concentration		
	Maximum Concentration	Time (hrs) of Maximum Concentration	Hrs 0-24	Hrs 25.5-48	Hrs 49.5-72	Hrs 0-24	Hrs 25.5-48	Hrs 49.5-72
Healthy Volunteers								
101								
102								
103								
104								
105								
106								
107								
109								
110								
111								
112								
113								
114								
115								
116								
Mean	127.8	11.2	116.9	129.1	125.4	11.6	35.2	59.0
Std.	63.3	1.78	61.1	55.9	50.7	2.97	2.65	2.17

SOURCE: KG/HHC\PK/EFF05 (May 24, 1996 14:57)

Table 5
AUC, Maximum Concentration, and Time
Acute Herpes Zoster and Post-Herpetic Neuralgia Patients

Patient	AUC	Maximum Concentration	Time (hrs) of Maximum Concentration	Sex	Weight	Age
Acute Herpes Zoster (HZ) Patients						
299	53334.0					
299	56619.0					
299	43596.0					
299	67738.5					
299	62982.0					
299	53802.0					
299	116491.5					
299	46305.0					
299	150525.0					
Mean	72377.0	82.5	13.3			
Std.	36447.0	43.3	1.58			
Post-Herpetic Neuralgia (PHN) Patients						
399	50130.0					
399	27324.0					
399	103149.0					
399	32067.0					
399	15867.0					
399	59886.0					
399	25713.0					
399	52146.0					
Mean	45785.3	52.1	13.9			
Std.	27712.2	30.6	5.54			

SOURCE: KG/HHC\PK/EFF02 (May 24, 1996 14:57)

Figure 1. Average Concentration a Function of Time

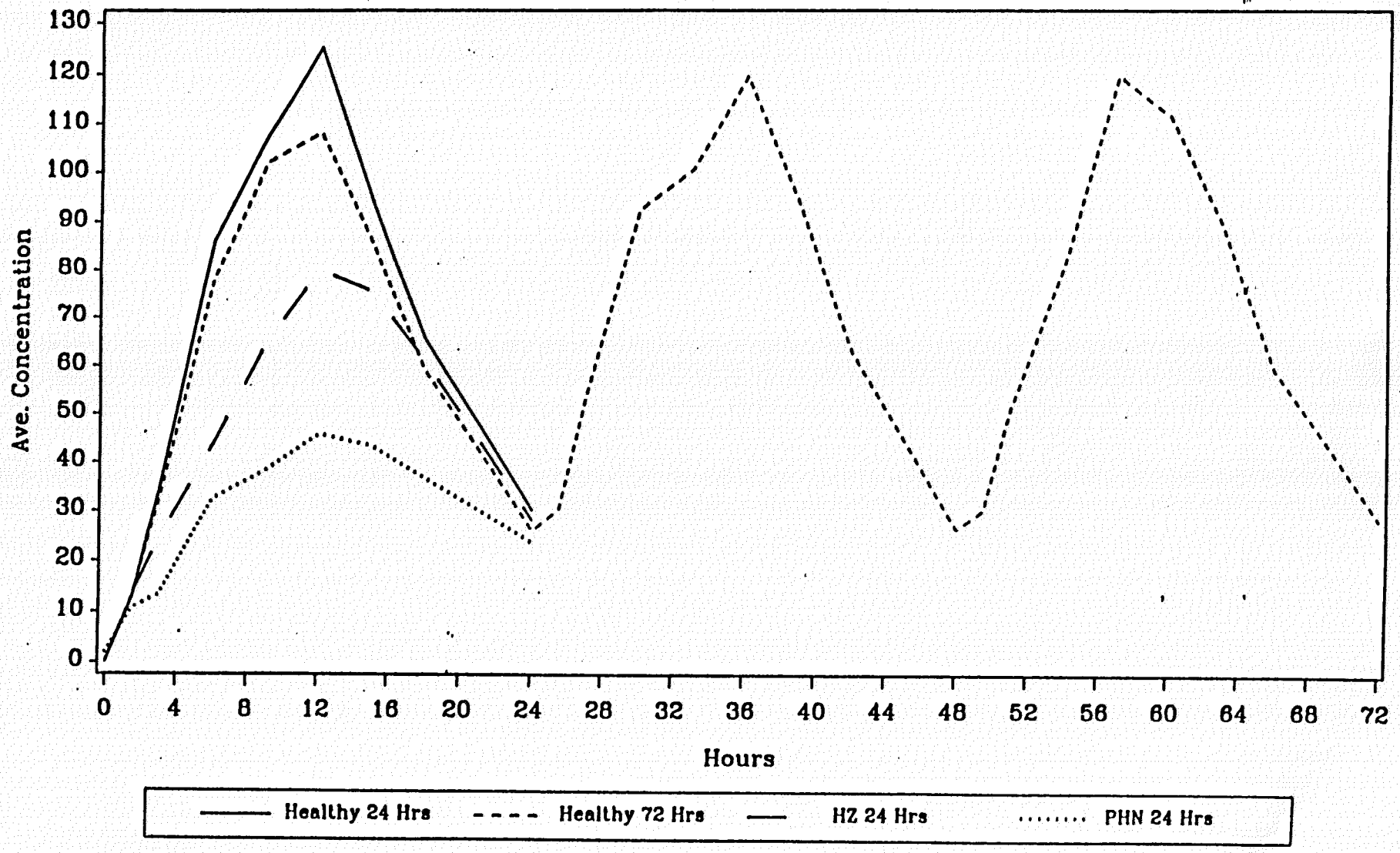


Figure 2. AUC as a Function of Age for Normal, HZ, and PHN Patients

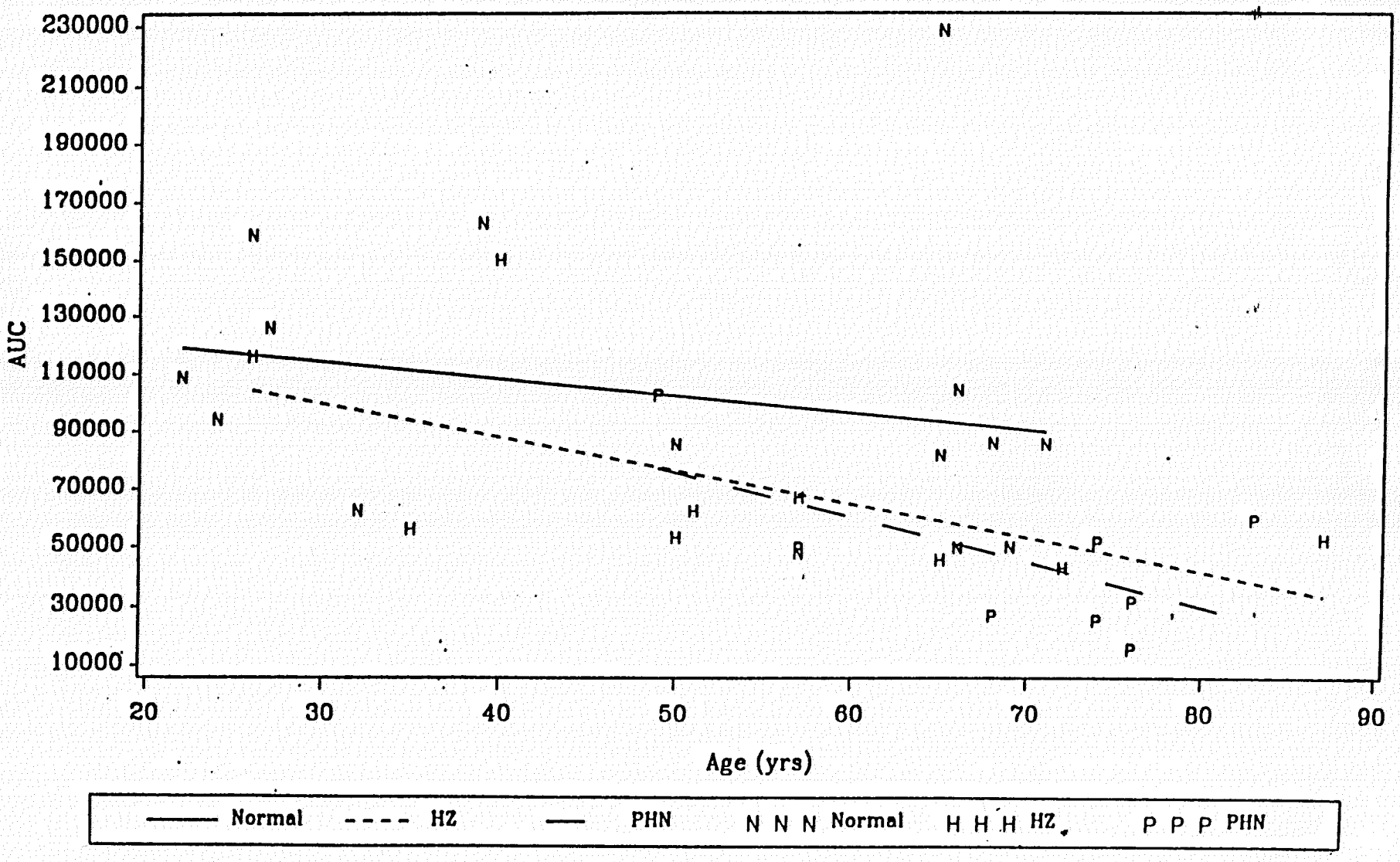
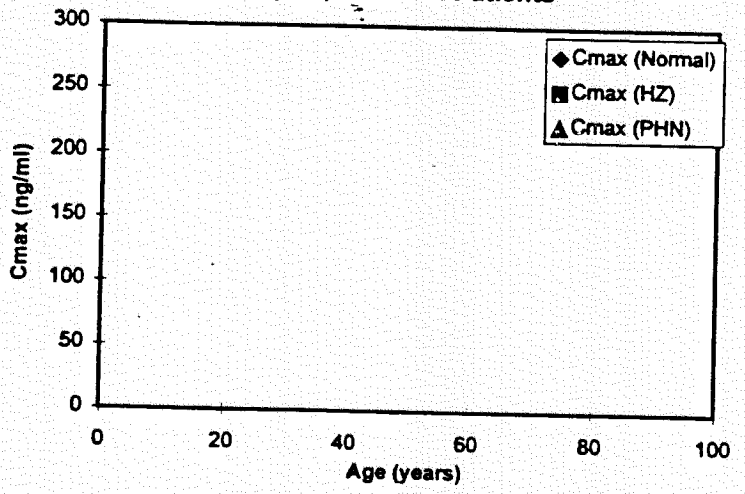


Figure 3. Cmax as a Function of Age for Normal, HZ, and PHN Patients



TITLE: Drug Delivery from Lidocaine Patch: Drug Permeation through Excised Rat Skin, Compared to Drug Release after Application to Human Skin VOLUME: 2.5

The purpose of this study was to examine any lot-to-lot variability (seven lots) with regard to permeation of lidocaine upon application of Lidocaine Patch to excised rat skin. Additionally, the drug release rate into the skin of human volunteers was examined using three lots of Lidocaine Patch, and the results compared to rat skin permeation data.

The in vitro study was conducted using excised rat skin. The amount of lidocaine diffused from the Lidocaine Patch through the rat abdominal skin into the receptor fluid was measured. Flux and lag-time were calculated for each diffusion cell, to determine any significant lot-to-lot differences in drug delivery. Seven lots were examined. Six skin samples were used for each lot. The results exhibited large unequal within lot variation. The calculated flux values ranged from 16.59 ± 1.55 to 29.38 ± 17.50 $\mu g/cm^2/hr$. The mean lidocaine permeation amount as a function of time are plotted in Figure 2 for each lot. The mean flux values and lag time along with their standard deviation are listed in Table 4.

The in vivo study were performed in 6 subjects for 3 lots. Lidocaine Patches were applied to the chest area of human volunteers. At 3, 6, 12 and 24 hours after application, a test patch was removed and the amount of residual lidocaine measured by and method. The amount of drug released from the patch into the skin was determined by subtraction from the initial drug content. The amount of drug released after application for each subject and lot are listed in Table 6 and the mean values are plotted in Figure 3. The data in Table 6 showed tremendous variability (within subject, between subject, within lot, and between lot).

In vitro and in vivo lidocaine release are compared in Table 8. The result from the in vitro study was not consistent with that from the in vivo. The sponsor indicated that the greatest source of inherent variability of the experimental models is the difference encountered with different skin, whether from different samples of excised skin from different rats, or the difference between application sites and between individual human volunteers. A statistical analysis was not performed since it is obvious that the standard deviations for flux are too large to show a statistical difference between mean values for particular lots of product.

In conclusion, the two experimental models employed in these studies were not able to differentiate between different lots of manufactured product on the basis of drug release of Lidocaine Patch.

Table 4. Flux and Lag Time (Mean ± S.D.)

Lot Number	Flux $\mu g/cm^2/hr$)	Lag Time (hr)
64041	26.02 ± 7.97	2.64 ± 0.31
64071	20.46 ± 4.42	3.40 ± 0.28
64072	16.59 ± 1.55	3.30 ± 0.23
81081	23.65 ± 9.77	2.26 ± 0.69
63072	27.61 ± 11.26	1.76 ± 0.63
34031	21.46 ± 7.52	2.01 ± 0.75
34032	29.38 ± 17.50	2.50 ± 0.49

Table 6. Drug Release after Application ($\mu g/cm^2$)

Lot Number	Subject No.	3 hrs	6 hrs	12 hrs	24 hrs
64041	1				
	2				
	3				
	4				
	5				
	6				
	mean	-14	28	50	215
	SD	107	50	116	134
64071	1				
	2				
	3				
	4				
	5				
	6				
	mean	57	87	100	262
	S.D.	47	109	105	193
64072	1				
	2				
	3				
	4				
	5				
	6				
	mean	22	95	150	322
	S.D.	77	82	124	197

Table 8. Comparison between in vivo and in vitro

	Lot Number	in vivo	in vitro
Flux ($\mu g / cm^2 / hr$)	64041	10.6	26.02 ± 7.97
	64071	9.6	20.46 ± 4.42
	64072	13.7	16.59 ± 1.55
Lag Time (hr)	64041	4.7	2.64 ± 0.31
	64071	-1.9	3.40 ± 0.28
	64072	0.5	3.30 ± 0.23

Figure 2. Lidocaine Permeation through Rat Skin (n=6)

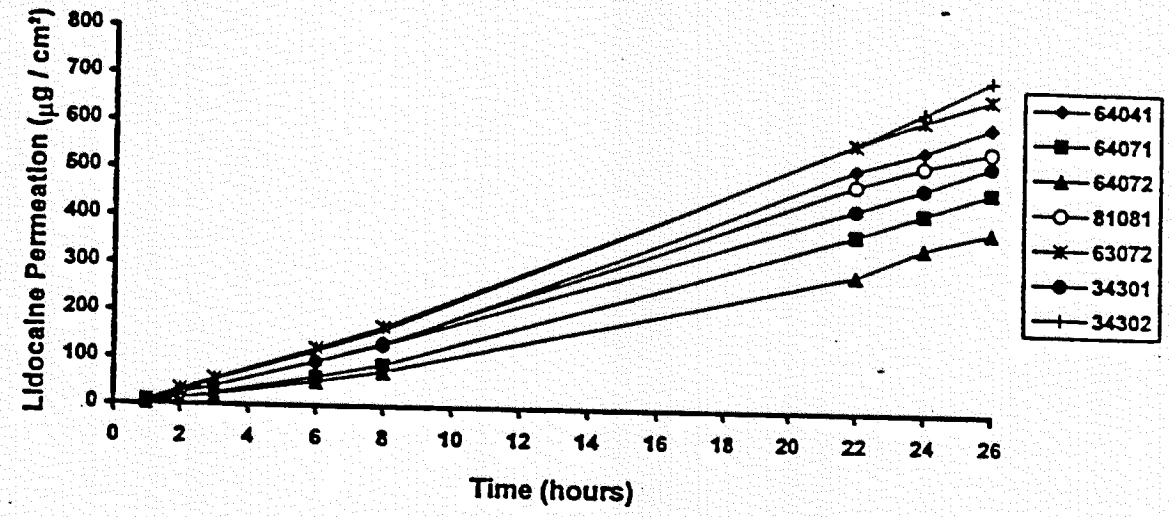
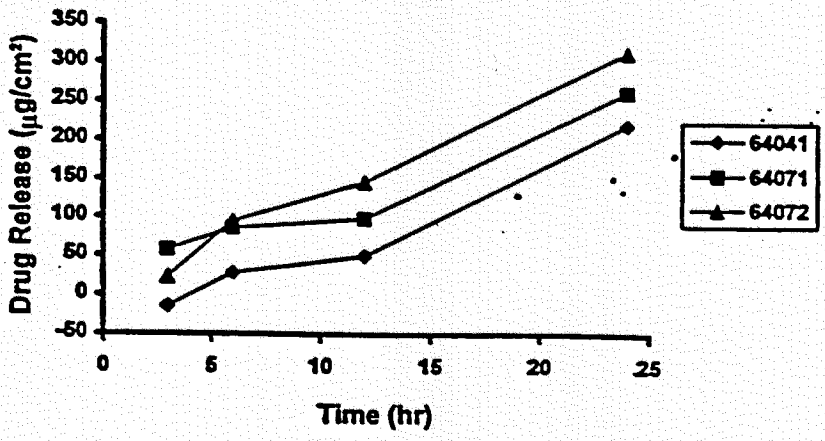


Figure 3. Lidocaine Release In Vivo (n = 6)



CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-612
PRODUCT: Lidocaine Patch, 5%
BRAND NAME: Lidoderm™ Patch
SPONSOR: Hind Health Care, Inc.
165 Gibraltar Court
Sunnyvale, CA 94089

SUBMISSION DATE: 8/30/97

REVIEWER: Dan Wang, Ph.D.

TYPE OF SUBMISSION: Amendment

In this amendment, the sponsor responded to non-approvable letter dated April 17, 1997 and addressed the deficiencies. The response to three biopharmaceutics comments are reviewed and summarized below.

Comment #1

The assay validation data for pharmacokinetic study were not included in this NDA. The sponsor should submit full assay validation report to the Agency.

Response:

The sponsor included the validation data in this submission.

Comment:

The validation data were reviewed and found acceptable.

Comment #2

In the section of "Overall Summary - Pharmacokinetics", reference is made to pharmacokinetic data collected in Phase 2 and 3 studies. Please submit these reports.

Response:

The sponsor indicated that these data were collected only to confirm that blood levels of lidocaine are very low during treatment with the patch. These data were not collected for pharmacokinetic purpose.

Comment:

All the blood concentration data collected in Phase 1, 2 and 3 studies should be submitted to the Human Pharmacokinetics and Biopharmaceutics section. However, it is not an approvability issue in this case.

Comment #3

Please submit in vitro release methods to determine the drug release rate through a membrane. Such method should be able to differentiate between lots of manufactured product on the basis of drug release and should serve as a specification for quality control.

Response:

The sponsor indicated that they are currently using the USP method, "Transdermal Delivery System – General Drug Release Standards", using Apparatus 5, found on pages 1796 and 1797 of USP 23, as a specification for drug release in the quality control of Lidocaine Patch. This test insures that the drug dissolved in the patch matrix is releasable from the patch, and this method is able to differentiate between different lots of product.

Comment:

The release method the sponsor mentioned above is also the method used for stability testing. The Agency (Chemistry reviewer) requested the sponsor to perform the drug release test at each time point. For each lot and at each stability testing period (0, 3, 6 and 9 month), drug release test was performed for Lidocaine Patch. Samples were taken at 10, 20, 30, 60, 120 and 180 minutes. The specification was 40% release at 30 minutes. The results of 0 month test showed an average (n=6) of 51.1, 52.6 and 51.75% release at 30 minutes for Lot No. 76062, 76063 and 76064, respectively. The percentage release at 180 minutes is 99.1, 99.1 and 97.2% for these three lots, respectively. This method is acceptable from biopharmaceutics point of review. See chemistry review for description of the release method and specification.

/S/

Dan Wang
Division of Pharmaceutical Evaluation III

8/17/98

FT initialed by D. Bashaw, Pharm.D. 8/17/98

cc:
NDA 20-612(Original)
HFD-550(Clinical, Koerner)
HFD-880(N. Fleischer, Bashaw, Wang)
HFD-870(Clarence Bott, Drug, Chron Files)
HFD-205(FOI)
HFD-344(Viswanathan)