CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-496

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Lidocaine HCl/Bupivacaine HCl
PRODUCT (Brand Name):	DUOCAINE™
DOSAGE FORM:	Ophthalmic Parenteral Injection
DOSAGE STRENGTHS:	[redacted]
NDA:	21-496
NDA TYPE:	4S
SUBMISSION DATE:	3/7/02
SPONSOR:	Amphastar Pharmaceuticals Inc.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	ODE V, HFD 550

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I. EXECUTIVE SUMMARY

Duocaine™ , contains the same active and inactive ingredients as listed for Astra Zeneca's Xylocaine (Lidocaine HCl injection, NDA 6-488) and Astra Zeneca's Sensorcaine (Bupivacaine HCl injection, NDA 18-304). The sponsor has submitted this submission as a 505(b)(2) application. No new clinical efficacy/safety or pharmacokinetic study has been performed to assess the bioavailability of the individual components of Duocaine.

I.1 RECOMMENDATION

A waiver request for conducting a biostudy with Duocaine™ has been accepted based on scientific reasons and the spirit of federal regulations that allow granting waivers for conducting biostudy with drug products. For details see discussions on page 4 of this review. The application is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

The labeling changes as provided on page 7 should be conveyed to the sponsor.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D._____

II. OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

II.1 BACKGROUND

Duocaine ([redacted] contains the same active and inactive ingredients as listed for Astra Zeneca's Xylocaine (Lidocaine HCl injection, NDA 6-488) and Astra Zeneca's Sensorcaine (Bupivacaine HCl injection, NDA 18-304). The sponsor has submitted this submission as a 505(b)(2) application. No new clinical efficacy/safety or pharmacokinetic study has been performed to assess the bioavailability of the individual components of Duocaine™. The sponsor is relying completely on literature studies for the approval of their combination product.

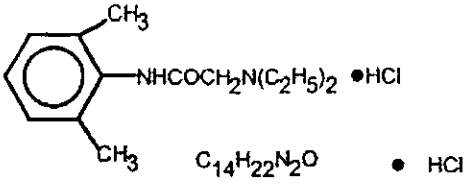
II.2 DRUG/DRUG PRODUCT INFORMATION

Dosage Form: Lidocaine HCl 1%, Bupivacaine HCl 0.375% ophthalmic solution for parenteral injection

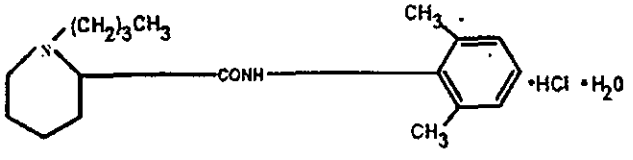
Indication: For the production of local and regional anesthesia for ophthalmic surgery by peripheral nerve block techniques such as parabulbar, retrobulbar, peribulbar and facial blocks

Pharmacologic Class: aminoacyl local anesthetic

Chemical Name: Lidocaine HCl, which is chemically designated as acetamide, 2-(Diethylamino)-N-(2, 6-dimethylphenyl)-monohydrochloride, as follows:



Bupivacaine HCl, which is chemically designated as 2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, as follows:



Dosage and administration:

- Peribulbar nerve block anesthesia, with and without epinephrine and/or hyaluronidase
- Retrobulbar and facial nerve block anesthesia, with and without epinephrine and/or hyaluronidase

Foreign marketing history: The combination product has not been marketed in any country. However, the individual products are marketed in the US

Formulation:

Ingredient	Amount per Ml
Lidocaine HCl, USP	10 mg
Bupivacaine HCl, USP	3.75 mg
Sodium Chloride USP	[redacted]
Hydrochloric acid, NF	As needed
Sodium Hydroxide, NF	As needed
Water for Injection, USP	Qs to 1 ml

II.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

II.3.1 Request for waiver of in-vivo biostudy with Duocaine Injection

Based on 21 CFR 320.25 (g) , for combination products, a sponsor is required to conduct a bioavailabilty study with the combination product compared to each active ingredients or therapeutic moities administered concurrently in separate single ingredient preparations. However, in this case the sponsor is requesting a waiver for conducting a study to demonstrate bioavailability/bioequivalence between the combination product and the two active ingredients when administered individually at the same time. However, under 21 CFR 320.22 none of the clauses allow for a waiver under current circumstances. Reason being:

- The combination product Lidocaine HCl injection 1%/Bupivacaine HCl injection 0.375%, is not the subject of approval of a full approved NDA. The regulations read that the active and inactive ingredients of the product should be the subject of a full approved NDA and should be present in the same concentration.
- Bupivacaine HCl injection 0.375% is not the subject of approval of a full approved NDA, however, Bupivacaine HCl injection 0.75% is diluted to 0.375% and is regularly used in clinical practice.

However, based on scientific reasons along with the spirit of regulations a waiver for conducting a biostudy can be granted in this circumstance based on the following reasons:

- The drug product is a parenteral solution solely to be administered by injection or an ophthalmic solution, hence, the bioavailability may be self evident.

- The drug product contains Lidocaine HCl injection 1%. This active ingredient is present in the same concentration and dosage form as the drug product that is the subject of an approval of full NDA [Astra Zeneca's Xylocaine™ NDA 6-488]. The drug product also contains ™ (Bupivacaine HCl injection 0.375%. The active and inactive ingredients are the same and proportionally similar to a drug product which is the subject of an approval of full NDA [Astra Zeneca's Sensorcaine™ 0.25%, 0.5% and 0.75%, NDA 18-304)]
- The drug product contains no inactive ingredients or other change in formulation from the drug product that is the subject of an approved NDA that may significantly affect absorption of the active drug ingredient. In Duocaine™, the inactive ingredients are Sodium Chloride, Sodium Hydroxide and Hydrochloric acid that are used for making the solution isotonic and for adjusting the pH to about 6.5, and as such will not affect systemic absorption of individual components.
- The sponsor has provided literature in which a pharmacokinetic study has been conducted with this combination product, hence bioavailability information from this product is available.
- Based on dicussion with Medical Officers, Drs William Boyd and Wiley Chambers, it was revealed that in the current clinical practice a total 10 mL solution of Lidocaine HCl, 1% and Bupivacaine HCl 0.375% has been administered together as proposed in this application for the past several years for local anesthesia.

Discussions regarding the regulatory approach for granting waiver in this situation were held with Dennis Bashaw (Team Leader) and John Lazor (Division Director, DPEIII)

11.3.2. Application consists of literature references and cross-references to approved NDAs 6-488 & 18-304:

The sponsor has submitted about 15 literature articles to support their application for the combination product. The label of Duocaine™ has been taken from the Xylocaine™ and Sensorcaine™ label. The pharmacokinetic parameters of lidocaine and bupivacine from the combination product have been taken from the reference by J.Barr (Barr J et.al, effects of adrenaline and hyaluronidase on plasma concentrations of lidocaine and bupivacaine after peribulbar anesthesia, British Journal of Anesthesia, 1995; 75: 692-7). Only this literature reference pertains to the same concentrations of lidocaine and bupivacaine as proposed in this application, hence, only this reference has been reviewed. The summary of this article as given by the sponsor has been attached in the Appendix to this review.

The overall conclusions from J. Barr's article is as follows:

- The inter-individual variability in the plasma concentrations was high (N=24).
- The mean peak concentrations of lidocaine and bupivacaine were reduced by 43% and 39%, respectively, in the presence of epinephrine (5 μg/mL). Epinephrine is used widely in regional anesthetic techniques to limit the rate of absorption of local anesthetics, to prolong anesthesia and to reduce toxicity.

- Hyaluronidase (75 iu/mL) did not have any affect on the peak plasma concentrations of either lidocaine or bupivacaine. Although, it is believed that hyaluronidase increases systemic absorption, this study did not show an increase in absorption. Hyaluronidase is also known to be active at pH 6.4-7.4. The pH of the solution used in this study was
  5.34. Hence, the authors propose that this lower pH could be a probable reason for seeing no significant effect in the absorption of the local anesthetics in the presence of hylauronoidase.

Relevant conclusions from other literature articles are:

- Even at a concentration of 2% lidocaine and 0.75% bupivacaine with 150 units of hyaluronidase after peribulbar administration, toxicity threshold was not attained (Ref: F Gao, Venous levels of lidocaine and bupivacaine after peribulbar block, Anesthesia, 1996; 51: 1109-12)
- Peribulbar administration of 2% lidocaine and 0.5% bupivacaine with 100 iu hyaluronidase showed a significantly shorter Tmax in the hyaluronidase group for both lidocaine (17.1 min vs 32.7 min) and bupivacaine (16.8 min vs 26.5 min) as compared to the control group with hyaluronidase. Cmax was not affected in the presence of hyaluronidase.(Ref: Nathan et.al, The role of hyaluronidase on lidocaine and bupivacaine pharmacokinetics after peribulbar blockade, Anesth Anal 1996; 82:1060-4)
- The pharmacokinetics of lidocaine and bupivacaine are unaltered in the mixture of the two in any combination (Ref: LT Seow et.al, Lidocaine and bupivacaine mixtures for epidural blockade, Anesthesiology, 1982; 56: 177-83)

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IV. APPENDIX I

IV.1 LITERATURE SUMMARY REPORT

Sponsor's Summary
Of the following Reference

Barr J et.al, effects of adrenaline and hyaluronidase on plasma concentrations of lidocaine and bupivacaine after peribulbar anesthesia, British Journal of Anesthesia, 1995; 75: 692-7

Study PKD# 6 - 007

1. Purpose of the Study:

To measure peak plasma concentrations produced by peribulbar block and the influence of the commonly used adjuvants, hyaluronidase and adrenaline, on peak plasma concentrations and area under the plasma concentration-time curves.

2. Settings:

Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB

3. Methods:

3.1 Patient Type:

Cataract Surgery

3.2 Drug Description:

A mixture of 1% lidocaine and 0.375% bupivacaine with hyaluronidase 1500 iu and epinephrine 100μg

3.3 Treatment Groups:

Twenty-four patients were allocated randomly to one of four groups:
(I) Local anaesthetic alone (lidocaine 10 mg ml^{-1}-bupivacaine 3.75 mg ml^{-1})
(II) Local anaesthetic with adrenaline (5 μ ml^{-1})
(III) Local anaesthetic with hyaluronidase (75 iu ml^{-1})
(IV) Local anaesthetic with adrenaline and hyaluronidase

3.4 Reference:

12. Barr J, Kirkpatrick N, Dick A, Leonard L, Hawksworth G, Nobel DW Effects of adrenaline and hyaluronidase on plasma concentrations of lidocaine and bupivacaine after peribulbar anesthesia. British Journal of Anesthesia 1995;75:692-7

4. Demographic Data:

Patient characteristics (mean (SD) [range] or number)

Group	n	Age (yr)	Weight (kg)	Sex (M/F)	ASA I/II/III
I	6	77.5 [71–87]	70.5 (16.1) [55–94]	3/3	3/3/0
II	6	74.2 [58–85]	69.8 (14.8) [53–87]	1/5	1/4/1
III	6	76.2 [61–96]	76.5 (16.5) [55–100]	4/2	1/5/0
IV	6	81.7 [72–91]	63.5 (5.8) [57–73]	1/5	1/5/0

5.3 Plasma Concentration - Time Curve

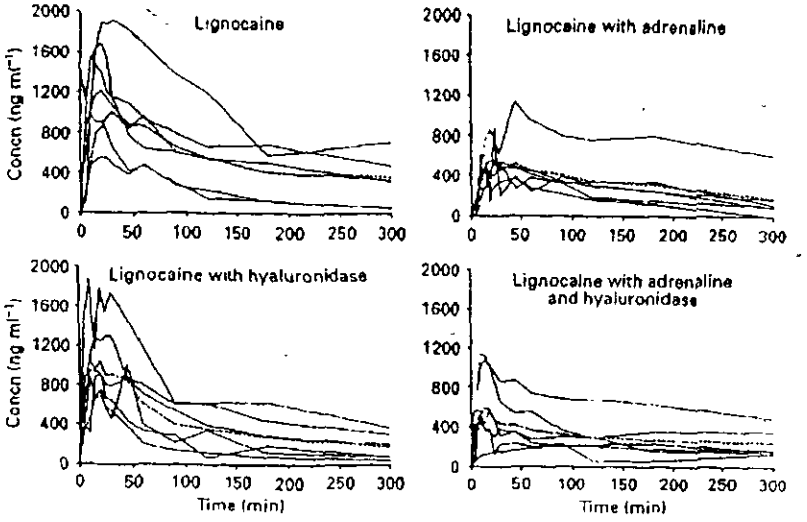

Figure 1 Individual lignocaine concentration–time curves for the four groups of patients (solid lines). Broken line = mean lignocaine concentration–time curve for each group.

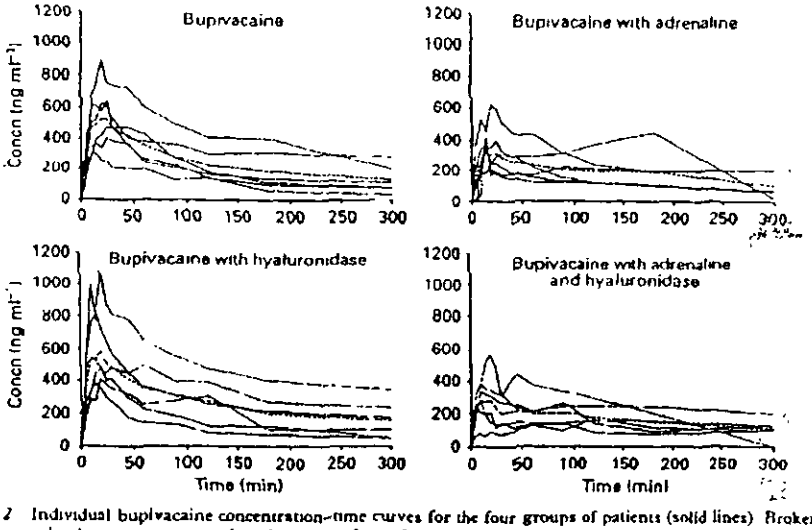

Figure 2 Individual bupivacaine concentration–time curves for the four groups of patients (solid lines). Broken line = mean bupivacaine concentration–time curve for each group.

5. Results and Discussions:

5.1 Efficacy of Peribulbar Block

Table 1

Details of block (mean (median) [range] or number)

Group	Top-up	Corneal anaesthesia at 15 min	Motor score at 15 min	Block adequacy	Complications
I	1/6	6/6	0.83 (0.5) [0–2]	6/6	1/6
II	0/6	6/6	0.5 (0.5) [0–1]	6/6	0/6
III	0/6	6/6	0.17 (0.00) [0–1]	6/6	0/6
IV	0/6	6/6	0.67 (0.5) [0–2]	6/6	0/6

Discussion:

All patients received a total of 10 ml of the local anaesthetic solution, except for one patient in group I who required supplementary injections of local anaesthetic (5ml) at 15 min (table 1).

5.2 Influence of Hyaluronidase and Adrenaline on Lidocaine Bupivacaine Pharmacokinetics

Table 2

Mean ((SD) [range]) peak concentrations ($C_p$max), area under the curve (AUC_{∞}) and time to peak plasma concentration (tC_pmax) of local anaesthetics. [a] Mean for group minus outlier

	$C_p$max (ng ml^{-1})		AUC_{∞} (ng ml^{-1} h)		tC_pmax (min)	
	Lignocaine	Bupivacaine	Lignocaine	Bupivacaine	Lignocaine	Bupivacaine
Group I	1287 (522) [550–1910]	552 (218) [300–900]	2913 (1497) [1226–5199]	1291 (536) [708–2141]	20 [12–30]	21 [13–33]
% Control	100%	100%	100%	100%		
Group II	707 (346) [530–1130]	387 (149) [210–630]	1633 (1061) [809–3730]	969 (474) [540–1825]	27 [13–45]	20 [15–25]
% Control	55%	70%	56%	75%		
Group III	1130 (433) [620–1810]	616 (283) [350–1090]	2006 (1149) [656–3799]	1305 (713) [558–2493]	22 [10–23]	21 [13–45]
% Control	88%	112%	69%	101%		
Group IV	670 (368) [230–1150]	327 (142) [160–570]	1509 (972) [718–3327]	793 (263) [528–1185]	41 (13[a]) [10–180]	29 (11[a]) [10–120]
% Control	52%	59%	52%	61%		

Table 3

Analysis of variance table for the effects of adrenaline and hyaluronidase on $C_p$max and AUC_{∞} for lignocaine and bupivacaine and the influence of the covariates of weight and volume of local anaesthetic

Lignocaine		Bupivacaine	
$C_p$max	AUC_{∞}	$C_p$max	AUC_{∞}
Adrenaline			
$F = 16.9$	$F = 10.1$	$F = 10.5$	$F = 8.1$
$P = 0.001$	$P = 0.005$	$P = 0.004$	$P = 0.011$
Hyaluronidase			
$F = 0.944$	$F = 2.4$	$F = 0.04$	$F = 0.41$
$P = 0.34$	$P = 0.14$	$P = 0.84$	$P = 0.53$
Covariates			
Weight			
$F = 5.4$	$F = 11.3$	$F = 3.2$	$F = 6.4$
$P = 0.03$	$P = 0.003$	$P = 0.09$	$P = 0.02$
Volume of local anaesthetic			
$F = 2.1$	$F = 1.5$	$F = 0.9$	$F = 0.9$
$P = 0.16$	$P = 0.24$	$P = 0.36$	$P = 0.37$

Discussions:

There was considerable variation in peak plasma concentrations of lidocaine and bupivacaine after peribulbar block (table 2, 3). The mean changes from control are presented in table 2. The mean peak concentration of lidocaine ($C_p$max) for the adrenaline groups was reduced to 57% of the non-adrenaline groups (P = 0.001). Hyaluronidase had no significant effect on the ($C_p$max) value of lidocaine (P = 0.34), where only a slight reduction to 90% was observed compared with the non-hyaluronidase groups (table 3). Similarly, the ($C_p$max) value of bupivacaine was reduced to 61% in the adrenaline groups compared with the non-adrenaline groups (P = 0.004). Hyaluronidase appeared to have no effect on ($C_p$max) (P = 0.84) (table 2, 3).

Discussions:

The area under the plasma concentration-time curves over the first 300 min (AUC_{300}) reflected the results for peak plasma concentrations. Adrenaline significantly reduced AUC_{300} for both local anaesthetics and produced a flattening of the plasma concentration-time curve (fig 1, 2). Hyaluronidase had no significant effect on AUC_{300}. Time *to peak plasma concentration (tC_pmax) was variable with no significant differences* attributable to adrenaline or hyaluronidase (tables 3, 4)

5.4 Toxicity Scores

The mean "toxicity scores" for groups I-IV were 0.6, 0.38, 0.61 and 0.34. Adrenaline group had significantly lower scores than *non*-adrenaline groups (P=0.001) but the effect of hyaluronidase was not significant (P=0.6). Although group scores suggested *a satisfactory margin of safety, one patient in group I had a toxicity score of* 0.95 and another in group III had a score of 1.0, although no patient in the study had symptoms or signs of toxicity. The maximum toxicity score of individuals in groups II and IV were 0.52 and 0.58.

The $C_p$max values for lidocaine and bupivacaine in the patient who required supplementary injections were 1010 ng ml^{-1} and 470 ng ml^{-1}, which calculated to a toxicity score of 50.

5.5 Corneal Anaesthesia and Motor Score

In terms of corneal anaesthesia and motor score there were no statistically *significant* differences between groups at 15 min (table 1). Block adequacy, as judged by the surgeon immediately before surgery, was deemed satisfactory in all cases. The only complication during the study was a lower lid hematoma in one patient (group I) which *did not prevent surgery from proceeding.*

6. *Conclusion:*

1. Although epinephrine reduced the *peak plasma concentrations* of lidocaine and bupivacaine by about 40% and hyaluronidase had no effect on that, the quality of anesthesia did *not differ between* groups.

2. The area under the plasma concentration-time curves *to* 300 *min* (AUC_{300}) behaved similarly. There was a reduction in AUC_{300} for lidocaine and bupivacaine in the epinephrine *groups, in contrast with no significant effects* of hyaluronidase on AUC_{300} for both anesthetic agents.

V. APPENDIX II

V.1 SPONSOR'S LABEL

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VI. APPENDIX I

VI.1 FILING-REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-496	Brand Name	DUOCAINE
OCPB Division (I, II, III)	III	Generic Name	
Medical Division	550	Drug Class	
OCPB Reviewer	Veneeta Tandon	Indication(s)	
OCPB Team Leader	Dennis Bashaw	Dosage Form	Ophthalmic parenteral injection
		Dosing Regimen	Peribulbar or retrobulbar
Date of Submission	3/7/02	Route of Administration	parenteral
Estimated Due Date of OCPB Review	July 02	Sponsor	Amphastar Pharmaceuticals
PDUFA Due Date	Jan 03	Priority Classification	
I. Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose.				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				

Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose.				
replicate design: single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	15	4		
Total Number of Studies				

Filability and QBR comments

II.	"X" if yes	Comments
III. Application filable ?	X	Reasons if the application is not filable (or "attachment if applicable.) For example, is clinical formulation the same as the to-be-marketed one?
IV. Comments sent to firm ? V.		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above	505(b)(2) application, no clinical studies performed, approval would be based on literature references	
Primary reviewer Signature and Date	Veneeta Tandon	
Secondary reviewer Signature and Date	Dennis Bashaw	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Veneta Tandon
7/23/02 01:51:17 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/23/02 05:48:57 PM
BIOPHARMACEUTICS

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