urine from untreated rats. No doxorubicin was detected in the feces, probably because of degradation of the fluorescent chromophore by intestinal microflora.[89]

6. Summary

The plasma pharmacokinetics of DOXIL and Adriamycin are different. The plasma concentration of doxorubicin may be up to 2000-fold higher in DOXIL-treated animals after intravenous injection of equivalent doses of DOXIL and Adriamycin. DOXIL has a significantly higher AUC and longer MRT, and a lower rate of clearance and volume of distribution compared to Adriamycin. The first phase of the biexponential plasma concentration-time curve is relatively short (half-life = 1 to 3 hours), and the second phase, which represents the majority of the AUC, is prolonged, with a half-life ranging from 20 to 30 hours. Depending on the method employed, more than 93% and perhaps more than 99.9% of the doxorubicin measured in plasma during the two phases is liposome-encapsulated[42,43] (LTI-30-93-27). Plasma doxorubicin concentration and AUC were dose-dependent after treatment with DOXIL, but plasma half-life, mean residence time, volume of distribution and clearance were not.

In contrast, the plasma pharmacokinetics of non-Stealth conventional liposomes are dose-dependent because of overload of liposome elimination mechanisms, probably temporary lipid saturation of the mononuclear phagocyte system (MPS) at higher lipid doses (for review see Senior, 1987[90]; Abra and Hunt, 1981[91]). Stealth liposomes are also removed from circulation by the MPS, but at a much slower rate owing to their surface-bound PEG molecules and apparently do not result in saturation at the doses used.[41,92] Even after repeat dosing of DOXIL in rats, which resulted in residual amounts of doxorubicin in the plasma, plasma pharmacokinetics remained independent of dose, indicating that saturation had not occurred. Multiple dosing at a longer dose interval in dogs avoided accumulation of doxorubicin in the plasma.

After a single intravenous dose of DOXIL, peak tissue concentrations of doxorubicin were lower and occurred later than after a single Adriamycin treatment. Doxorubicin persisted in the tissues in DOXIL-treated animals owing to the slower clearance of liposome-associated drug. Tumor levels were higher in DOXIL-treated animals after equivalent doses of DOXIL and Adriamycin. Doxorubicin levels rose in tissues of rats with repeated dosing of DOXIL, but tissue levels remained dose-proportional even at the end of the dosing period, suggesting that saturation of tissues had not occurred. No accumulation of drug was seen in the heart, and, despite the apparent accumulation of doxorubicin in other tissues after multiple DOXIL treatments, no evidence of increased toxicity of DOXIL was observed in the toxicology portion of the repeated dose study, with the exception of cutaneous lesions. Doxorubicin concentrations were higher in the

lesions than in normal skin in rats and dogs, but decreased rapidly as the lesions healed, approaching levels seen in normal skin by five weeks after the last dose. In the multiple dose studies in rats and dogs, DOXIL was less cardiotoxic and marginally less myelotoxic than was an equivalent dose of Adriamycin. The decreased relative toxicity of DOXIL is believed to be due to the decreased peak concentration of free, non-liposomal doxorubicin in the plasma and tissues of treated animals.

TABLE 18

SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD) C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_s (mL)
Single Dose										
LTI-30-94-15	Rat/ Sprague Dawley/4M	DOXIL 3	1.0	1	[redacted]	29.1±0.5	λ_1: 3.9±0.3 λ_2: 28.0±1.4	691±4	0.35±0.0	14.7±1.1
		DOXIL 3	1.0	1		26.4±0.9	λ_1: 1.8±0.9 λ_2: 23.9±3.0	652±72	0.39±0.04	13.3±1.6
		DOXIL 3	1.0	1		27.2±1.9	λ_1: 0.5±0.2 λ_2: 18.2±1.8	587±52	0.41±0.03	10.7±0.5
		DOXIL 3	1.0	1		28.1±2.4	λ_1: 1.0±1.1 λ_2: 23.6±0.9	783±23	0.37±0.02	12.7±0.3
LTI-30-94-15 MPEG Study 1		2% MPEG[a]	1.0	1		27.7±1.2	λ_1: 0.7±0.1 λ_2: 20.0±1.1	589±45	0.50±0.04	14.6±0.7
		5% MPEG[a]	1.0	1		31.5±0.7	λ_1: 1.3±0.7 λ_2: 24.1±1.5	780±69	0.37±0.03	13.0±0.8
		7% MPEG[a]	1.0	1		24.2±1.2	λ_1: 2.0±1.5 λ_2: 21.4±3.0	472±40	0.52±0.04	16.2±1.7
LTI-30-94-15 MPEG Study 2		2% MPEG[a]	0.3	1		7.4±0.2	λ_1: 0.5±0.5 λ_2: 15.9±0.5	138±8	0.55±0.03	12.5±0.5
		7% MPEG[a]	0.3	1		8.0±0.2	λ_1: 1.6±0.8 λ_2: 20.2±1.4	169±9	0.50±0.02	14.5±1.3

[a] Mole % of MPEG-DPSE in DOXIL formulation tested.

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TABLE 18 (cont.)
SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_s (mL)
LTI-30-94-15	Rat/ Sprague Dawley/4M	48% Chol.[a]	1.0	1	[redacted]	26.9±0.4	λ_1: 0.5±0.2 λ_2: 24.0±0.8	782±26	0.37±0.01	12.7±0.2
LTI-30-94-15 Particle Size Study 1		96 nm[b]	1.0	1		26.4±0.6	λ_1: 0.3±0.2 λ_2: 18.8±1.6	578±50	0.46±0.04	12.5±0.7
		144nm[b]	1.0	1		28.4±1.5	λ_1: 1.2±1.5 λ_2: 18.1±3.9	483±35	0.55±0.04	14.3±2.2
		187 nm[b]	1.0	1		30.2±1.9	λ_1: 3.4±0.8 λ_2: 28.0±2.3	393±1	0.67±0.01	27.7±2.1
		217 nm[b]	1.0	1		31.3±2.3	λ_1: 1.8±0.4 λ_2: 20.7±4.4	300±32	0.89±0.09	26.7±6.4
LTI-30-94-15 Particle Size Study 2		96 nm[b]	0.3	1		7.2±0.5	λ_1: 3.4±1.7 λ_2: 24.4±3.1	155±9	0.49±0.02	17.0±1.6
		121 nm[b]	0.3	1		7.7±0.3	λ_1: 1.6±0.9 λ_2: 22.0±2.5	150±6	0.58±0.04	18.6±3.2
		158 nm[b]	0.3	1		7.6±0.2	λ_1: 3.9±0.6 λ_2: 18.2±1.2	106±65	0.74±0.05	19.3±0.8

[a] Mole % of cholesterol in DOXIL formulation tested.
[b] Mean particle size of formulation, as determined by dynamic light scattering techniques.

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TABLE 18 (cont.)
SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_d (mL)
LTI-30-94-15 LPC	Rat/ Sprague Dawley/ 4M	4% LPC[a]	1.0	1	[redacted]	26.3±1.8	λ_1: 1.0±0.02 λ_2: 22.6±1.6	564±84	0.46±0.05	15.5±2.4
		9% LPC[a]	1.0	1		25.3±1.5	λ_1: 1.0±0.4 λ_2: 21.4±4.1	456±78	0.63±0.07	19.8±5.3
		11% LPC[a]	1.0	1		21.9±2.0	λ_1: 2.3±1.9 λ_2: 22.8±1.8	444±18	0.58±0.04	18.9±2.4
		18% LPC[a]	1.0	1		21.0±2.1	λ_1: 0.9±0.5 λ_2: 20.7±3.2	409±63	0.62±0.06	18.3±1.4

[a] Mole % of lysophosphatidylcholine (LPC) in DOXIL formulation tested.

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TABLE 18 (cont.)
SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (Means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	$V_{ß}$ (mL)
LTI-30-93-27	Rat/ Sprague Dawley/ 4M	DOXIL 3	1.0	1	[redacted]	22.5±0.9	λ_1: 2.8 λ_2: 25.5	595	0.45	16.8
		DOXIL 3 (lipo.)[a]	NA[b]	NA		21.4±0.8	λ_1: 2.9 λ_2: 25.7	579	0.47	17.3
LTI-30-92-14	Rat/ Sprague Dawley/ 4M	DOXIL 3	0.3	1		8.1±0.3	λ_1: 1.2±1.0 λ_2: 21.4±1.5	184±22	0.44±0.07	14.6±2.2
		DOXIL 2	0.3	1		8.4±0.6	λ_1: 1.9±0.5 λ_2: 21.9±0.8	203±11	0.38±0.03	12.5±1.1

[a] Liposome-encapsulated doxorubicin, determined after Dowex separation of free and liposomal doxorubicin (see Methods section, Report No. LTI-30-93-27).
[b] NA = not applicable.

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TABLE 18 (cont.)
SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_s (mL)
LTI-30-92-06	Rat/ Sprague Dawley/ 4-6M	DOXIL 2	0.3	1	[redacted]	7.6±0.3	λ_1: 4.0±2.0 λ_2: 29.1±8.1	232±34	0.35±0.05	14.3±1.5
		DOXIL 2	0.3	1		7.6±0.5	λ_1: 2.3±1.9 λ_2: 23.0±4.4	175±13.4	0.41±0.03	13.7±2.3
		DOXIL 1	0.3	1		4.4±0.3	λ_1: 0.5±0.1 λ_2: 17.4±0.6	81±6	0.90±0.06	22.5±1.5
		DOXIL 1	0.3	1		5.5±0.2	λ_1: 0.8 λ_2: 16.2	92.9	0.83	19.3
		DOXIL 1	0.3	1		4.3±0.2	λ_1: 4.4±2.2 λ_2: 34.9±17.1	115±25	0.66±0.14	30.6±9.9
		DOXIL 1	0.3	1		5.9±0.6	λ_1: 3.3 λ_2: 21.1	121	0.70	21.2
		DOXIL Res[a]	0.3	1		8.0±0.4	λ_1: 1.0 λ_2: 19.5	183	0.46	12.8
		DOXIL Res[a]	0.3	1		6.7±0.6	λ_1: 1.5 λ_2: 21.7	153	0.50	15.7
		DOXIL Res[a]	0.3	1		6.4±0.2	λ_1: 5.0±1.8 λ_2: 34.2±17.1	167±21	0.40±0.05	18.5±7.3

[a] Research formulation of DOXIL; identical to DOXIL 1 but formulated with 250 mM ammonium sulfate, rather than 155mM.

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TABLE 18 (cont.)

SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_s (mL)
LTI-30-93-06	Rat/Sprague Dawley/4M	DOXIL 2	4.0	1	[redacted]	121.2±9.0	λ_1: 3.6±2.0 λ_2: 30.2±4.0	2650±164	0.34±0.02	12.2±2.5
		DOXIL 2	8.0	1		196.7±20.1	λ_1: 0.95±0.4 λ_2: 27.4±5.5	5715±769	0.32±0.05	15.4±5.0
		DOXIL 2	12.0	1		311.9±30.4	λ_1: 1.2±0.3 λ_2: 27.2±6.5	8012±911	0.34±0.04	13.2±2.9
		DOXIL 1	4.0	1		86.7±5.4	λ_1: 0.95±0.3 λ_2: 19.7±1.6	1409±121	0.63±0.06	18.1±1.9
		DOXIL 1	8.0	1		160.9±24.5	λ_1: 0.8±0.9 λ_2: 14.6±8.6	3224±263	0.56±0.05	15.4±0.39
		DOXIL 1	12.0	1		289.9±29.8	λ_1: 0.4±0.2 λ_2: 19.2±1.7	4482±357	0.60±0.05	16.3±1.40
LTI-30-93-23[a]	Rat/ Sprague Dawley/ 3M, 3F	DOXIL 3	1.0	1		15.1±0.7[c]	27.7	605	0.41	16.5
		Adria[b]	1.0	1		0.01±0.01[c]	1.9	0.2	10869	30193
LTI-30-93-28	Rabbit/ NZW/4M	DOXIL 3	1.5	1		19.2±0.4	λ_1: 0.5±0.1 λ_2: 21.3±2.0	368±59	6.0±1.1	176±17
		Adria[b]	1.5	1		0.9±0.1	λ_1: 0.03±0.002 λ_2: 4.0±0.7	0.8±0.1	2536±299	13651± 1028

[a] See results of tissue distribution study below.
[b] Adriamycin RDF™ (Adria Laboratories).
[c] First time point was 30 minutes post-dose, which prevented the precise determination of plasma PK.

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TABLE 18 (cont.)
SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ± SD)				
						C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_β (mL)
LTI-30-93-07	Dog/ Beagle/ 3M	DOXIL 2	1.5	1	[redacted]	27.7±4.5	λ_1: 0.2±0.1 λ_2: 25.9±3.5	656±59	15.5±1.6	595±85
		DOXIL 1	1.5	1		27.9±7.9	λ_1: 0.6±0.9 λ_2: 21.6±1.8	463±120	24.0±8.5	747±274
Repeat Dose										
LTI-30-93-24[a]	Rat/ Sprague Dawley/ 4M, 4F	DOXIL 3	0.25	1	[redacted]	3.8±0.5[c]	17.6 ±	100	0.54	13.5
		DOXIL 3	1.0	1		17.4±2.7[c]	20.3	433	0.49	16.3
		Adria.[b]	1.0	1		0.01±0.002[c]	6.6	0.13	1643	14940
		DOXIL 3	0.25	13		7.4±0.6[c]	32.7	346	0.26	12.9
		DOXIL 3	1.0	13		22.4±3.0[c]	33.3	1011	0.30	14.8
		Adria.[b]	1.0	13		0.02±0.004[c]	9.5	9.5	1572	22454

[a] See results of tissue distribution study below.

[b] Adriamycin RDF™ (Adria Laboratories).

[c] First time point was 30 minutes post-dose, which prevented the precise determination of plasma PK.

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TABLE 18 (cont.)

SUMMARY TABLE OF NONCLINICAL PLASMA PHARMACOKINETIC STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Pharmacokinetic Parameters (means ±SD) C_{max} (µg/ml)	$T_{1/2}$ (hr)	AUC∞ (mg/L·hr)	CL (mL/hr)	V_s (mL)
LTI-30-94-18	Dog/Beagle/ 6M, 6F	DOXIL 3	0.25, 0.75, 1	10	[redacted]	No measurable doxorubicin or doxorubicinol in pre-dose samples. Assay LLOQ = 5 n/mL.				
		Adria.[a]	1	10		No measurable doxorubicin or doxorubicinol in pre-dose samples. Assay LLOQ = 5 ng/mL.				
DOXIL 1										
LTI-30-91-04	Rat/ Sprague Dawley/3M	DOXIL 1	6	1	[redacted]	134.1±6.9	λ_1: 0.03 λ_2: 25.2	3055	0.48	17.9
		Adria.[a]	0.9	1		5.8±0.5	λ_1: 0.16 λ_2: 29.1	11.1	24.3	1013.5
LTI-30-93-05	Rat/ Sprague Dawley/3M	DOXIL 1	0.3	1		7.0±0.6	λ_1: 0.9±0.8 λ_2: 16.4±2.0	102±3.3	0.78±0.03	18.6±2.8
		DOXIL 1	6	1		130.5±4.4	λ_1: 1.3±0.4 λ_2: 18.7±2.5	2143±150	0.74±0.1	19.9±1.8
		DOXIL 1	0.3	1		8.3±0.6	λ_1: 1.7±0.7 λ_2: 19.4±1.8	141±12	0.57±0.1	16.0±2.8
		DOXIL 1	6	1		152.4±3.6	λ_1: 1.1±0.4 λ_2: 17.7±1.7	2736±165	0.58±0.04	14.7±0.8

[a] Adriamycin RDF™ (Adria Laboratories).

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TABLE 19

SUMMARY TABLE OF NONCLINICAL TISSUE DISTRIBUTION STUDIES WITH DOXIL

Report No.	Species/ Strain/ Group size	Drug	Dose (mg/kg)	No. of Doses	Lot No.	Results
Single Dose						
LTI-30-94-11	Mouse/ Balb/c (C26 tumor-bearing)/ 3M	DOXIL Adria.[a]	6.0	1	[redacted]	• Tumor levels peaked at 24 hr in DOXIL group, 1 hr in Adriamycin group. • Tumor AUC 7-fold greater in DOXIL group.
LTI-30-93-15	Mouse/ Swiss nude (PC-3 human xenograft)/ 2M	DOXIL Adria.[a]	0.9	1		• Tumor levels peaked at 24 hr in DOXIL group and 4 hr in Adriamycin group. Dox concentration in tumor 3×higher at 4 hr, 80× higher at 24 hr. • Tumor AUC 25-fold higher in DOXIL group.
LTI-30-93-23	Rat/ Sprague Dawley/ 3M, 3F	DOXIL 3 Adria.[a]	1.0	1		• Peak levels in most tissues at 30 min in Adriamycin group and 24 hr in DOXIL group. • Peak levels higher in Adriamycin group in all but spleen, bone marrow and duodenum. • Slower elimination of drug from tissues in DOXIL-treated rats. • Tissue AUCs higher in DOXIL treated animals.
Repeat Dose						
LTI-30-93-24	Rat/ Sprague Dawley/ 4M, 4F	DOXIL 3 Adria.[a]	0.25, 1.0	13	[redacted]	• Peak tissue levels at first time point (1 day post-dose) in all 3 groups. • Tissue levels and AUCs highest in 1.0 mg/kg DOXIL group and, except for liver and spleen, tissue levels lowest in 0.25 mg/kg DOXIL group. • Tissue AUCs: 1.0 DOXIL >0.25 DOXIL >1.0 Adriamycin. • Accumulation, but not saturation, seen in tissues of DOXIL-treated rats.

[a] Adriamycin RDF™ (Adria Laboratories).

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Nonclinical ADME Reports Referenced

Nonclinical Plasma Pharmacokinetics Studies:

Report Number: LTI-30-94-15
Report Title: Plasma Pharmacokinetics of DOXIL (Stealth liposomal doxorubicin HCl) Injection and DOXIL Formulation Variants in Rats after a Single Dose
Report Date: [redacted] 19[redacted]
Toxicology Cross Reference: None
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-27
Report Title: Determination of Total and Liposome-Associated Doxorubicin in Rats after a Single Intravenous Dose of DOXIL (Stealth liposomal doxorubicin HCl) Injection
Report Date: [redacted] 19[redacted]
Toxicology Cross Reference: None
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-14
Report Title: Comparison of Plasma Pharmacokinetics of DOXIL-250/Tris and DOXIL 250/Histidine after a Single Intravenous Injection in Rats
Report Date: [redacted] 19[redacted]
Toxicology Cross Reference: None
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-92-06
Report Title: Comparison of the Plasma Pharmacokinetics of DOXIL-155 and DOXIL-250 after a single Intravenous Injection in Rats
Report Date: [redacted] 19[redacted]
Toxicology Cross Reference: None
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Nonclinical ADME Reports Referenced (continued)

Report Number: LTI-30-93-06
Report Title: Single Dose Plasma Pharmacokinetics Study of DOXIL-155 and DOXIL-250 in Rats
Report Date: [redacted]19[redacted]
Toxicology Reference: LTI-30-92-11
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-28
Report Title: Plasma Pharmacokinetics of DOXIL (Stealth liposomal doxorubicin HCl) Injection and Adriamycin in New Zealand White Rabbits.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: None
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-07
Report Title: Comparison of Plasma Pharmacokinetics of DOXIL-155 and DOXIL-250 after a Single Intravenous Injection in Dogs.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: LTI-30-92-13
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-94-18
Report Title: Doxorubicin Concentration in Skin and Plasma after Multiple Doses of DOXIL in Dogs.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: LTI-30-94-07
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Nonclinical ADME Reports Referenced (continued)

Nonclinical Plasma Pharmacokinetic Studies with DOXIL 1:

Report Number: LTI-30-93-05
Report Title: Single Dose Plasma Pharmacokinetics of DOXIL (Stealth Liposomal Doxorubicin Hydrochloride Injection) in Rats.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: None
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-91-04
Report Title: Single Dose Plasma Pharmacokinetics of Stealth Liposomal Doxorubicin-Hydrochloride Injection in Rats.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: None
Report Author: [redacted]Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Tissue Distribution Studies:

Report Number: LTI-30-94-11
Report Title: Tissue Distribution of Doxorubicin in C26 Colon Carcinoma-Bearing Mice after Treatment with DOXIL and Adriamycin.
Report Date: [redacted]19[redacted]
Report Author: [redacted]Liposome Technology, Inc.
Study Site: [redacted]
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-15
Report Title: Tissue Distributions and Therapeutic Effects of Intravenous Liposomal and Free Doxorubicin Against Human Prostatic Carcinoma Xenografts.
Report Date: [redacted]19[redacted]
Toxicology Cross-Reference: None
Report Author: [redacted]
Study Site: [redacted]
DOXIL Lot No.: [redacted]

Nonclinical ADME Reports Referenced (continued)

Report Number: LTI-30-93-23
Report Title: Tissue Distribution and Plasma Pharmacokinetics of Doxorubicin after a Single Intravenous Dose of DOXIL in Rats.
Report Date: [redacted] 19[redacted]
Toxicology Cross-Reference: LTI-30-93-09
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]

Report Number: LTI-30-93-24
Report Title: Tissue Distribution and Plasma Pharmacokinetics of DOXIL after Multiple Dosing in Rats.
Report Date: [redacted] 19[redacted]
Toxicology Cross-Reference: LTI-30-93-08
Report Author: [redacted] Liposome Technology, Inc.
DOXIL Lot No.: [redacted]