CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s000

NON-CLINICAL REVIEW(S)

`DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209112
Supporting document/s:	SD:1(eCTD:0000)
Applicant's letter date:	08/31/ 2016
CDER stamp date:	09/02/ 2016 (SD:1)
Product:	Ascor® (Ascorbic Acid)
Indication:	Treatment of scurvy
Applicant:	McGuff Pharmaceuticals, Inc.
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer:	Parvaneh Espandiari, PhD
Supervisor/Team Leader:	C. Lee Elmore, PhD
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1 Executive Summary

1.1 Introduction

McGuff Pharmaceuticals, Inc. (the Applicant) is seeking marketing approval of Ascor® (Ascorbic Acid Injection, USP 500mg/mL) for the treatment of scurvy in (b) (4) as a 505(b)(2) new drug application. To support product safety and justify marketing approval of Ascorbic Acid Injection from the nonclinical point of view, the Applicant is relying on published literature.

Previously, two ascorbic acid injection products have been marketed in the United States, including Cenolate (since 1938) and Ascor L 500 (since 2002). Both drugs were withdrawn voluntarily in 2010 to comply with FDA's Unapproved Drug Initiative. Cenolate and Ascor L 500 had similar intravenous dosages for adult and pediatric patients, as follows: adults - 50 to 200 mg/day for dietary supplementation; 4 to 12 g/day in 3 to 4 divided doses for urinary acidification; 100 to 250 mg once or twice daily for a minimum of two weeks for scurvy (i.e., up to 500 mg/day); and pediatric patients - 35 to 100 mg/day for dietary supplement; 500 mg every 6 to 8 hours for urinary acidification; 100 to 300 mg/day in divided doses for a minimum of two weeks for scurvy.

Ascorbic acid is a generally recognized as safe (GRAS) substance by the oral route and is included as an excipient in multiple FDA approved drug products, as a chemical preservative in foods, and alone or as a combination of marketed dietary supplement ingredients. Ascorbic acid is also a component of the active pharmaceutical ingredient (API) of approved, marketed multivitamin injectable products [e.g., at 200mg in Infuvite Adult for injection (NDA 021163) and Infuvite Adult for Infusion (NDA 021559); and at up to 80 mg in Infuvite Pediatric for injection (NDA 021265) and Infuvite Pediatric for infusion (NDA 021646)].

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were conducted to support this 505(b)(2) marketing application for Ascorbic Acid Injection.

In general, findings from nonclinical studies in different species as reported in the public literature by different routes of administration at up to 2500 mg/kg (body weight) and for duration at up to 2 years, as they relate to the safety pharmacology, chronic repeat-dose toxicity, mutagenicity or carcinogenicity, and reproductive/developmental toxicology studies, suggest no safety concerns for the proposed (b) (4) recommended clinical doses in adults, children and infants and safety margins support the proposed doses. Ascorbic acid is not considered to be genotoxic. While no carcinogenicity study was performed with the product, concern for tumorigenicity for Ascorbic Acid Injection is very low for the following reasons: the API in Ascorbic Acid

Injection is chemically identical to vitamin C obtained through the diet, the treatment duration for scurvy is short-term, and carcinogenicity studies in rodents at high oral doses were negative. Reproductive toxicity potential for Ascorbic Acid Injection is low, based on available nonclinical literature data. No adverse effects were observed in rats or mice administered supraphysiologic doses of ascorbic acid from mating, through the period of embryo-fetal development, parturition and throughout the lactation period to weaning.

No toxicologic concerns regarding excipients, impurities/degradants, or leachables/ extractables were identified.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of Ascorbic Acid Injection.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Suggestions for the pharm/tox related sections:

Section 8.1 Pregnancy

Under (b) (4)

(b) (4)

(b) (4)

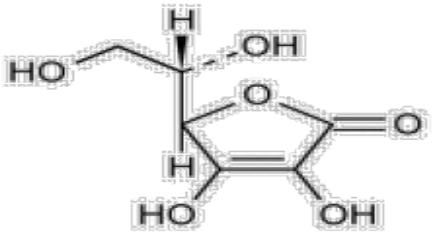
Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 50-81-7
Generic Name: Ascorbic Acid Injection, USP
Brand Name: Ascor
Chemical Name: (2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one
(IUPAC) L-ascorbic acid
Molecular Formula/Molecular Weight: $C_6H_8O_6$/176.1241
Structure or Biochemical Description:



Pharmacologic Class: Vitamin C

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND: 076483
DMF: (b) (4)

2.3 Drug Formulation

Ascorbic Acid Injection contains the active ingredient of ascorbic acid (USP 500 mg/mL) and the inactive ingredients of edetate disodium (USP (b) (4) sodium bicarbonate (USP), water for injection (USP), (b) (4) (NF), and sodium hydroxide (NF, for pH adjustment), as shown in the table below.

Table 1: Ascorbic Acid Injection, USP

Constituent	Function	Final Composition per mL
Sodium Ascorbate	Active Ingredient	562.5 mg of Sodium Ascorbate (Equivalent to 500 mg of Ascorbic Acid)
Sodium Bicarbonate	(b) (4)	--
Edetate Disodium	(b) (4)	0.25 mg
Sodium Hydroxide	pH adjustment	(b) (4) pH 5.6 - 6.6
Water for Injection	(b) (4)	(b) (4)

Applicant's table

The Applicant referred to DMF # (b) (4) for (b) (4) and noted that all components of their formulation are with USP/NF standards. Moreover, the Applicant noted that all inactive ingredients are below the FDA Inactive Ingredient Database (IID) drugs for IV infusion:

Table 2: Ascorbic Acid Injection - Inactive Ingredient

INGREDIENT	FORMULATION TARGET FOR ASCORBIC ACID INJECTION, USP	IID LEVELS (IV INFUSION) INJECTION
Edetate Disodium, USP	(b) (4)	1%
Sodium Bicarbonate, USP		82%
Sodium Hydroxide, NF		13%

Applicant's table

Note: levels of edetate disodium and sodium bicarbonate are different in the FDA Inactive Ingredient Database (IID) than that reported values by the Applicant. Yet, there are no safety concerns for these inactive ingredients as they appear in the Applicant's formulation because their values are still within range of the FDA IID drugs.

2.4 Comments on Novel Excipients

There are no novel excipients in the drug formulation.

2.5 Comments on Impurities/Degradants of Concern

The Applicant reported impurities for the final drug product as presented in the table below:

Table 3: Ascorbic Acid Injection- USP Release and Stability Specifications for Assay and Related Substances

Property/Characteristic	Method	Requirement/Specification
Assay	CM121/M370-0035 or CON-IM-0912	(b) (4)
Related Substances (b) (4)	CON-IM-0912	NMT (b) (4) NMT NMT NMT NMT

Applicant's table

In (b) (4) Ascorbic Acid Injection, the total levels of impurities are (b) (4) %, higher than acceptable limits based on ICH Q3A and Q3B qualification thresholds ((b) (4) % = (b) (4) mg = (b) (4) µg/day vs. (b) (4) µg/day for a single injection). A risk analysis was performed for these impurities based on the available nonclinical and clinical data. Findings from these data suggest that there are no safety concerns with levels of these impurities in a single administration of Ascorbic Acid Injection. The safety data for these impurities are as summarized below:

(b) (4)

(b) (4)

Applicant's figure

(b) (4)

Other Impurities: The proposed levels of other impurities, (b) (4) (NMT (b) (4) % or (b) (4) mg) and other unidentified impurities (NMT (b) (4) % or (b) (4) mg) are within acceptable threshold for (b) (4) daily dose of (b) (4) of proposed Ascorbic Acid Injection based on ICH Q3B(R2) Impurities in Drug Product.

[1] *Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. Nutr Rev. 1999; 57:71–7.*
[2] *Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med. 2004;140:533–7.*
[3] *McEvoy, CT., Schilling, D., Clay, N., et al. (2014). Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. JAMA, 311(20), 2074-2082.*
[4] *Massey, LK., Liebman, M., Kynast-Gales, S. A. (2005). Ascorbate increases human oxaluria and kidney stone risk. The Journal of Nutrition, 135(7), 1673-1677.*
[5] *Taylor, E. N., & Curhan, GC. (2004). Role of nutrition in the formation of calcium-containing kidney stones. Nephron Physiology, 98(2), 55-p63.*
[6] *Robitaille L, Mamer, OA, Miller WH, Levine M, Assouline S, Melnychuk D, Rousseau C, Hoffer LJ. (2009) Oxalic acid excretion after intravenous ascorbic acid administration. ScienceDirect, Metabolism, 58(2) 263-269.*
[7] *Asplin J.R. Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin North Am, 31 (2002), pp. 927-949.*

Extractable/Leachable: The Applicant reported a list of extractables/leachables in the drug product and reported that levels of these compounds are within acceptable levels.

Table 4: Ascorbic Acid Injection - Detected Leachable Study

Compound Category	Compounds Observed	Concentration (µg/ml)
(b) (4)		< (b) (4) µg/ml
		< (b) (4) µg/ml
		(b) (4)
		approx. (b) (4) µg/ml
		approx. µg/ml

* Note: Although (b) (4) and (b) (4) were observed in samples tested by ICP analysis, these compounds are not categorized as leachables because similar values were found in (b) (4) and therefore concluded that these compounds were controlled excipient impurities (See Report Q17E1202 in Module 3.2.P.2 for discussion.)

Applicant's table

2.6 Proposed Dosing Regimen

IV administration with strength(s) of 25 g/50 mL (500 mg/mL) intended for:

(b) (4)

2.7 Regulatory Background

- On May 20, 2011, a pre-IND meeting was requested and written responses were granted (see nonclinical-related question for PIND meeting):

  "Sponsor Question: Does the Agency concur that the data provided in the Nonclinical Overview will support an NDA approval for the proposed (b) (4) *without further need for Nonclinical data?*

  FDA Response: The proposed approach of planned submission of published literature supporting nonclinical safety is acceptable. These publications should be submitted with your NDA for review. Further nonclinical studies will not be needed provided the submitted CMC data provides adequate characterization of (b) (4) *."*

- On August 1, 2014, the Sponsor requested a type C meeting and the telecommunication meeting was granted on October 16, 2014 to discuss the proposed clinical study (no nonclinical issues were discussed).

3 Studies Submitted

No GLP nonclinical studies were submitted. This application relies on published literature.

3.3 Previous Reviews Referenced

PT review #1 under IND 076483 (DARRTS, 03/06/2015)

4 Pharmacology

4.1 Primary Pharmacology

No nonclinical pharmacology studies were submitted.

Ascorbic acid (vitamin C) is a water soluble vitamin that is an essential dietary component. Primates are unable to synthesize ascorbic acid because they lack the enzyme L-gulonolactone oxidase. Ascorbic acid is found in foods and is available as a dietary supplement.

In the body, ascorbic acid is required for many biochemical functions, including the following: the biosynthesis of collagen (part of connective tissue), tyrosine metabolism, conversion of folic acid to folinic acid, carbohydrate metabolism, synthesis of lipids/proteins, iron metabolism, resistance to infections, and cellular respiration.

Deficiency of ascorbic acid intake causes scurvy, which is characterized by bleeding gums, tooth loss and gingivitis (early signs), multiple hemorrhages, muscle/ joint pain, tiredness, weakness, irritability, and weight loss.

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted.

In the body, ascorbic acid is involved in oxidation-reduction, collagen formation, change in iron absorption, transport, and storage and metabolism of folic acid[8], and biosynthesis of some amino acid and hormones. Ascorbic acid acts as an antioxidant and is implicated as playing a role in processes such as aging, inflammatory damage, wound healing, immune response, cataract prevention, cancer prevention/ treatment, and cholesterol metabolism [9,10,11].

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[8] Gosiewska, A., Mahmoodian, F., Peterkofsky, B. (1996). Gene expression of iron-related proteins during iron deficiency caused by scurvy in guinea pigs. Archives of biochemistry and biophysics, 325(2), 295-303.
[9] Friedrich, W. (1988). Wilhelm Friedrich Vitamin C. In Vitamins. Walter de Gruyter Berlin, New York.
[10] Gershoff, S. N. (1993). Vitamin C (ascorbic acid): new roles, new requirements. Nutrition reviews, 51(11), 313-326.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted.

Findings from submitted published literature are summarized in the following section:

Nervous System: Ascorbic acid is an antioxidant and may act as a neuroprotective agent by regulating dopamine- and glutamate-mediated neurotransmission (converting dopamine to norepinephrine), modulating glutamate transmission and neuronal maturation[12, 13]. Ascorbic acid regulates levels of neurotransmitter receptors, the function of glutamatergic and dopaminergic neurons and synthesis of glial cells and myelin[14, 15]. There are no known safety issues with IV ascorbic acid administration for the nervous system.

Cardiovascular system: Ascorbic acid is involved in the formation, maintenance, and repair of blood vessels. In a study using the guinea pig burn/wound healing model, ascorbic acid was tested at up to14.2 mg/kg/h. Findings of this study suggested no significant differences in heart rates, blood pressure, and cardiac outputs until 6 hour after injury[16] (after 6 hours, these values were lower in the control group). Therefore, available nonclinical data do not indicate a safety issue for the cardiovascular system with IV ascorbic acid administration.

Gastrointestinal System: In humans, the tolerable upper intake level of ascorbic acid is 2 g/day for adults[17]. At higher levels, ascorbic acid causes osmotic diarrhea and gastrointestinal disturbances. However, diarrhea was not reported in the clinical study in patients with solid tumors that were treated at 51-187g of IV ascorbic acid for four days/week up to 4 weeks[18]. There are no known safety issues with available data for the GI tract with IV ascorbic acid administration.

Renal Pharmacology: Ascorbic acid is excreted by the kidneys through filtration and active tubular reabsorption. In general, high dose oral doses of ascorbic acid do not increase oxalic acid (created via metabolism of ascorbic acid) excretion and renal stone

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[11] NIH Office of Dietary Supplements 2013.
[12] Friedrich, W. (1988). Wilhelm Friedrich Vitamin C. In Vitamins. Walter de Gruyter Berlin, New York.
[13] Harrison, FE., May, J. M. (2009). Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. Free Radical Biology and Medicine, 46(6), 719-730.
[14] Englard, S., & Seifter, S. (1986). The biochemical functions of ascorbic acid. Annual review of nutrition, 6(1), 365-406.
[15] Katsuki, H. (1996). Vitamin C and nervous tissue in vivo and in vitro aspects. In Subcellular Biochemistry. Springer US.
[16] Sakurai, M., Tanaka, H., Matsuda, T., Goya, T., Shimazaki, S., & Matsuda, H. (1997). Reduced resuscitation fluid volume for second-degree experimental burns with delayed initiation of vitamin C therapy (beginning 6 h after injury). Journal of Surgical Research, 73(1), 24-27.
[17] IOM 2000 Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids
[18]Stephenson, CM., Levin, RD., Spector, T., & Lis, CG. (2013). Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. Cancer chemotherapy and pharmacology, 72(1), 139-146.

formation[19, 20]. However, the high IV dose of ascorbic acid administration can reach to high levels of oxalate, which could cause oxalate crystallization in the urinary space (acute oxalate nephropathy) and formation of renal stone [21,22,23]. However, based on results of the phase 1 clinical study by Robitaille et al., (2012)[24], with ascorbic acid infused for 0.1 to 1.5 g/kg (b) (4), the proposed IV dose of (b) (4) ascorbic acid is unlikely to develop oxalate nephrocalcinosis and calcium oxalate stones. There are no known safety issues with available data with IV ascorbic acid administration for the renal system.

Respiratory System: There are no known safety issues with IV ascorbic acid administration for the respiratory system.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK/TK or ADME studies were submitted.

In the body, metabolism, excretion, and distribution of ascorbic acid are well understood. Ascorbic acid is reversibly oxidized to dehydroascorbic (DHA) and in humans is primarily excreted in urine. Ascorbic acid accumulates in the body in ranges from 300 mg (at near scurvy) up to 2 g. See table below for ascorbic acid synthesis and turn-over in different species:

Table 5: Ascorbic Acid - Different Species Synthesis and Turn-Over

Species	Ascorbic acid synthesis (mg/24h)		Half-life	Fractional turn-over rate
	Per animal	Per 100 g bw	Days	% of body pool catabolized in 24 h
Man	0	0	8-40*	3-4%
Guinea pig	0	0	3.6-4.0	17-20
Mouse	3.7	12.5	1.4	50
Rat	6-9	2.5-3.0	2.4-2.9	24-29
Rabbit	19.5	0.5	3.9	18
Golden Hamster	2.1	2.0	2.7	26

* Depending on the intake of exogenous ascorbic acid

Applicant's table

[19] *Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. Nutr Rev. 1999;57:71–7.*
[20] *Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med. 2004;140:533–7.*
[21] *McEvoy, CT., Schilling, D., Clay, N., et al. (2014). Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. JAMA, 311(20), 2074-2082.*
[22] *Massey, LK., Liebman, M., Kynast-Gales, S. A. (2005). Ascorbate increases human oxaluria and kidney stone risk. The Journal of Nutrition, 135(7), 1673-1677.*
[23] *Taylor, E. N., & Curhan, GC. (2004). Role of nutrition in the formation of calcium-containing kidney stones. Nephron Physiology, 98(2), 55-p63.*
[24] *L. Robitaille, O.A. Mamer, W.H.J. Miller, M. Levine, S. Assouline, D. Melnychuk, C. Rousseau, L.J. Hoffer. Oxalic acid excretion after intravenous ascorbic acid administration. Metabolism, 58 (2009), pp. 263-269.*

Ascorbic acid metabolism in different species with different routes of administration and duration present in the table below:

Table 6: Ascorbic Acid - Metabolism in Different Species

Species	Study	Route/ Dose	Duration	Results	Ref.
Guinea pigs	Metabolic (determine catabolic differences in acute and chronic deficient animals)	IP-(14)C-AA	275 days (high dose or normal dose ascorbic acid); then totally deficient or chronic deficiency (3 mg/kg/day) for 44 or 68 days, respectively.	Animals treated with long-term high dose ascorbic acid (86g/kg/day for 275 days) then subjected to chronic or acute ascorbic acid deficiency showed increased catabolism of the labeled ascorbic acid to respiratory (14)CO_2 compared to control animals maintained on 2g/kg for 275 days prior to deficiency.	(Sorensen 1974)
Rat/Guinea pig	ADME	IP-(14)C-AA	--	14C Recovery: 80-87 total body; 48% to 63% (urine) and 0.2% and 0.43% (feces).	(Takenouchi 1966)
Primates	Metabolic (determine urine metabolites with varying degrees of ascorbic acid supplementation)	Oral (14)C-AA		At low ascorbate intake (<10 mg/kg bw), unmetabolized ascorbic acid accounted for 10-20% and oxalate for 25-48% of the urinary excreted radioactivity. At higher intakes (>10 mg/kg bw), unmetabolized ascorbate (about 75%) was identified as the major fraction; oxalate contributed only 7% suggesting the metabolic conversion of ascorbate to oxalate to be limited.	(Tillotson 1981)

Species	Route/Dose	Duration	Results	Reference
Rat-albino Wistar	IP-labeled AA: 6.23, 1.45, 1.46, and 0.49 mg	--	Body pool 10.7 mg/100 g bw. Urinary excretion accounted for a fraction (15%) of the ascorbic acid excretion with renally excreted metabolites; remaining ascorbic acid was in excreted via the lungs as CO_2	(Burns 1954)
Rats	IP- 1.5 to 5.9 mg of (14)C-labeled ascorbic acid	24 hours	19% to 29% was converted to CO_2 and only 0.4% was excreted as oxalic acid in the urine	(Curtain and King 1955)
Rat/Guinea pig	PO-ascorbic acid (25 uCi)	48 hours	Peak excretion time in rats was 2 to 3 hr following oral administration and was 30 min in guinea pigs.	(Schmidt 1983)
Rat/Guinea Pig	IP-14C labeled AA	--	14C eliminated was in the range of 48% to 63% of administered in urine and 0.2% and 0.43% in feces. 5.5% of the 14C administered was detected in CO_2 (guinea pig) and 1.2-3.9% (rats) in 24h.	(Takenouchi 1966)

Applicant's table

Oral ascorbic acid absorption and distribution in tissues is regulated by active transport and simple diffusion from the gastrointestinal tract; however, IV ascorbic acid is distributed directly in tissues via the blood. Ascorbic acid's plasma levels upon oral absorption demonstrate an inverse dose-dependency (saturation of plasma levels up to 100 µmol/L); therefore, doses greater than 1 g are absorbed at less than 50%. However, Ascorbic acid's plasma levels with IV administration can reach up to 20 mmol/L with doses of 200 g (100 fold higher compared to the oral administration) [25, 26]. In a study

[25] *Graumlich JF, Ludden TM, Conry-Cantilena C, Cantilena LR, Jr, Wang Y, Levine M. Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. Pharm Res 1997; 14:1133–1139.*
[26] *Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996; 93:3704–3709.*

with both administration of IV and oral ascorbic acid of 1.25 g, plasma concentrations upon IV administration were about 4-fold higher compared to oral administration (oral: 134.8 ± 20.6 µmol/L vs. IV: 885 ± 201.2 µmol/L)[27].

6 General Toxicology

No nonclinical toxicity studies were conducted by the Applicant with Ascorbic Acid Injection.

Repeat-Dose Studies: Ascorbic acid has been investigated in repeat-dose toxicity studies in different species by different routes of administration. Findings from these studies are summarized in the table below:

Table 7: Ascorbic Acid - Repeat-Dose Toxicity Studies

Species	Dose	Route	Duration	Major findings reported
Mice[28]	500-1000 mg/kg	Oral, SC, IV	7 Days	None
Guinea Pigs [29 30]	400-2500 mg/kg	Oral, SC, IV	6 days	None
Rats[31]	0, 1, 10, 100 mg per 100 g bw	IV	21 days	At 10 and 100 mg, inhibitory effect on the pituitary-thyroid system based on changes on levels of thyroid hormones/TSH
Rats [32]	Up to 27.3 g/kg	Oral	10 weeks	NOAEL: 10 g/kg (based on mortality at 27.3g/kg)
Guinea Pigs [33]	Up to 250 mg	Oral	20 weeks	None
Mice/Rats [34]	0-100,000 ppm	Oral	14 days	None
Mice/Rats [35]	0-100,000 ppm	Oral	13 weeks	At 50,000 ppm, one mouse died (day 84) Reduced body weight gains: female rats started at 25,000 ppm; male mice started at 50,000 ppm

[27] Padayatty, SJ., Sun, H., Wang, Y., Riordan, HD., Hewitt, S. M., Katz, A., ... & Levine, M. (2004). Vitamin C pharmacokinetics: implications for oral and intravenous use. Annals of internal medicine, 140(7), 533-537.
[28] Demole, V. (1934). On the physiological action of ascorbic acid and some related compounds. Biochemical Journal, 28(3), 770.
[29] Demole, V. (1934). On the physiological action of ascorbic acid and some related compounds. Biochemical Journal, 28(3), 770.
[30] Kieckebusch, W., Griem, W., Lang, K. (1963). Studies on chronic toxicity of ascorbic acid in rats. Z Ernahrungswiss, 4, 5-14.
[31] Marcusen, D. C., and Heninger, R. W. (1976). Effect of ascorbic acid on the pituitary-thyroid system in the rat. J Endocrinol, 70(2),313-4.
[32] Kieckebusch, W., Griem, W., Lang, K. (1963). Studies on chronic toxicity of ascorbic acid in rats. Z Ernahrungswiss, 4, 5-14.
[33] Nandi, BK., Majumder, AK., Subramanian, N., & Chatterjee, I. B. (1973). Effects of large doses of vitamin C in guinea pigs and rats. The Journal of nutrition, 103(12), 1688-1695.
[34] National Toxicology Program 1983, National Toxicology Program Technical Report 247 Carcinogenesis Bioassay of L-Ascorbic Acid (Vitamin C) (CAS No. 50-81-7) in F344/N Rats and B6C3F1 Mice (Feed Study).
[35] National Toxicology Program 1983, National Toxicology Program Technical Report 247 Carcinogenesis Bioassay of L-Ascorbic Acid (Vitamin C) (CAS No. 50-81-7) in F344/N Rats and B6C3F1 Mice (Feed Study).

				Cystic endrometrial glands and myelofibrosis in females rats at 100,000 ppm Femur bone marrow (reticulum-cell hyperplasia) in: 2/10 female rats at 25,000 ppm; 1/10 female rats at 50,000 ppm; 4/10 female rats at 100,000 ppm Myeloid depletion in 2/10 female rats at 50,000 ppm and in 4/10 female rats at 100,000 ppm
Rats[36]	0-50,000 ppm	Oral	13 weeks	None

To support the safety of IV dosing with ascorbic acid, the disease animal models in dogs and cats were used at up to 2 g (every 24 hours) for 3-6 days. Results of these studies were not consistent. One study reported an anaphylactic reaction in one dog (1/8 with 2 infusions, but that recovered), and another dog with diarrhea (1/8 with 3rd infusion, which recovered) [37]. Another study with dogs at up to 2.5 g/day (IV infusion for 3-6 days) reported with no treatment-related effects and an improvement in clinical signs and symptoms of distemper [38].

7 Genetic Toxicology

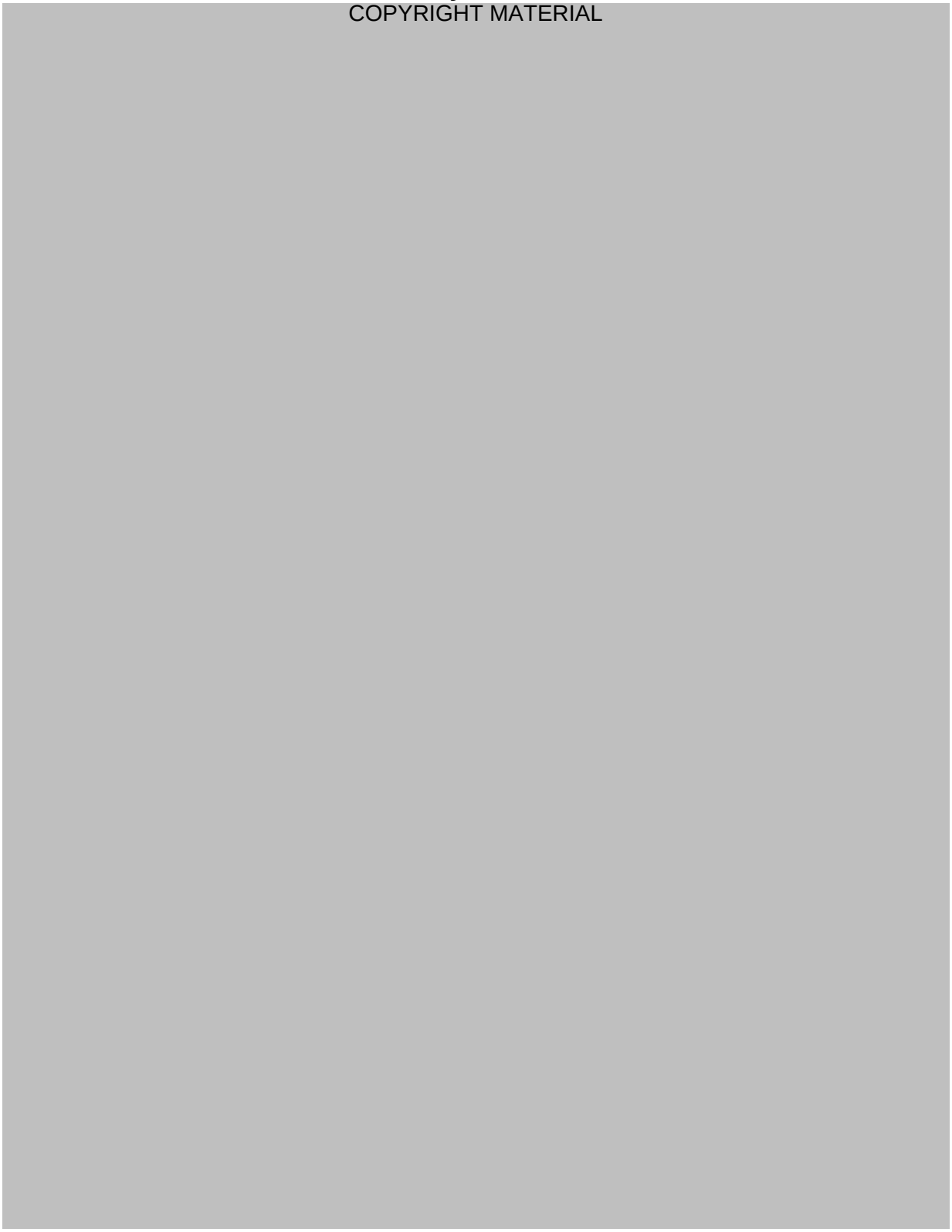
No genotoxicity studies were conducted by Applicant.

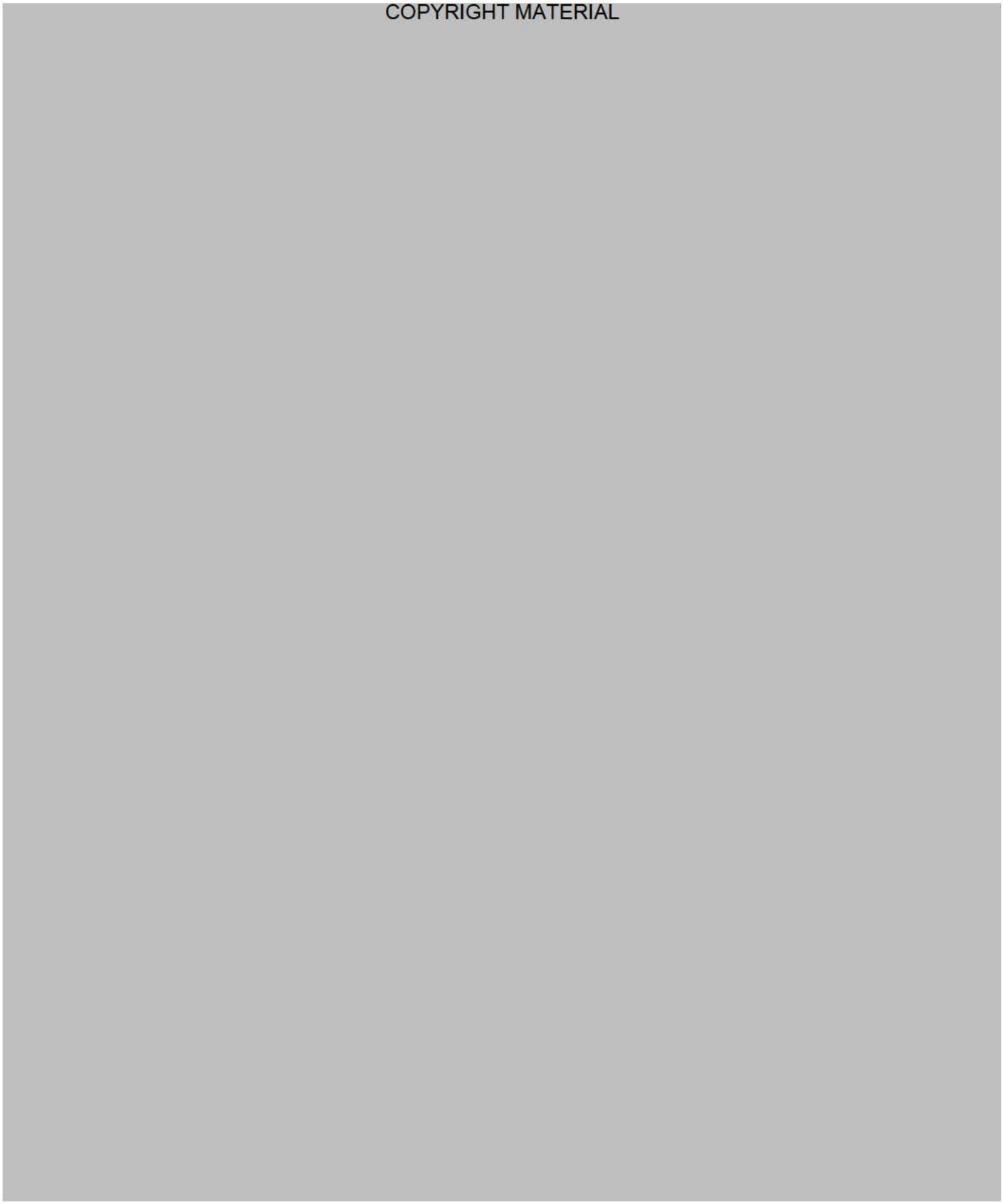
Results of genetic toxicity studies with ascorbic acid suggest that ascorbic acid is not genotoxic.

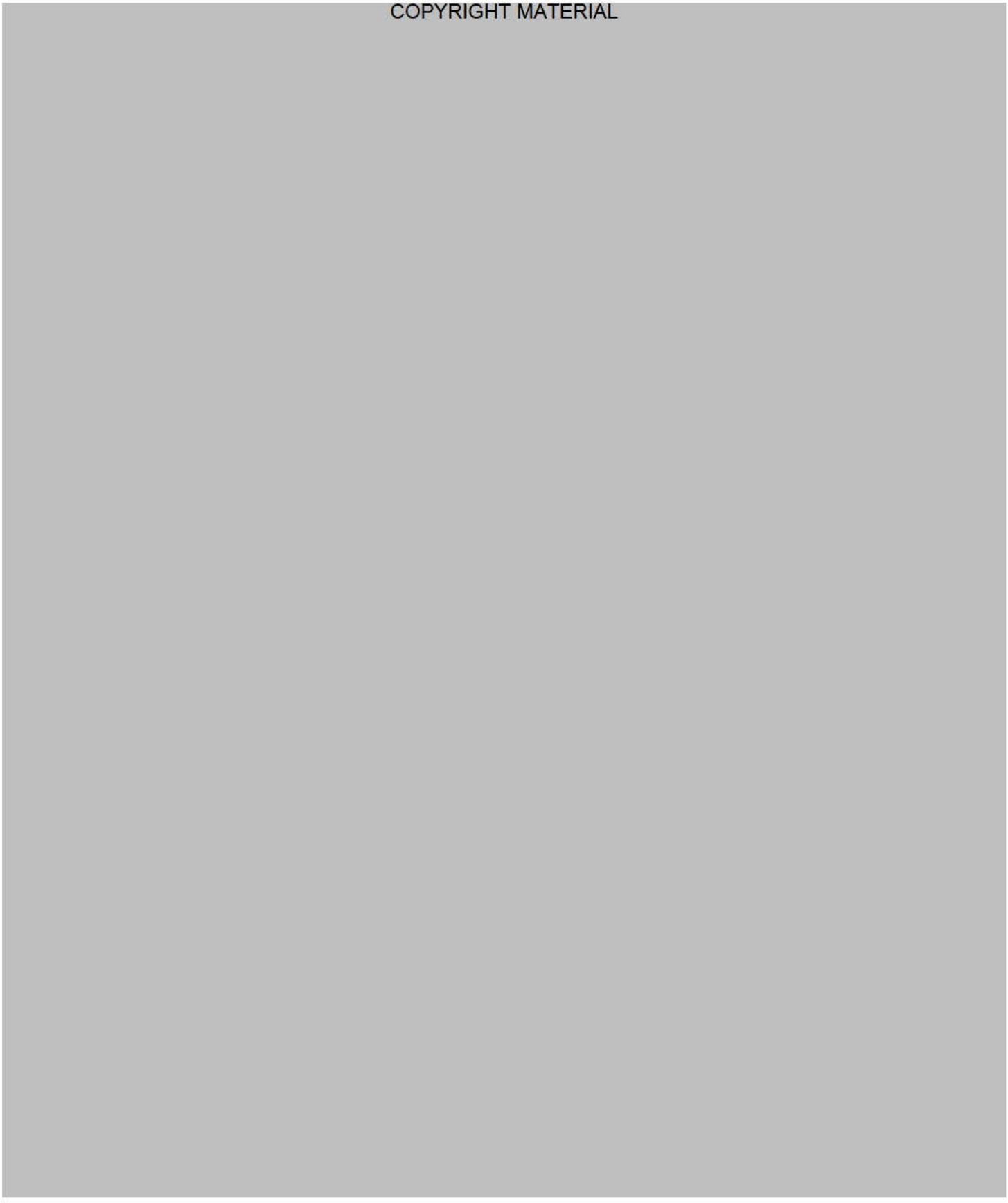
Tables below show results of *in vitro* and *in vivo* genotoxicity studies (submitted by the Applicant and as reproduced from the Cosmetic Ingredient Review) **[39]**:

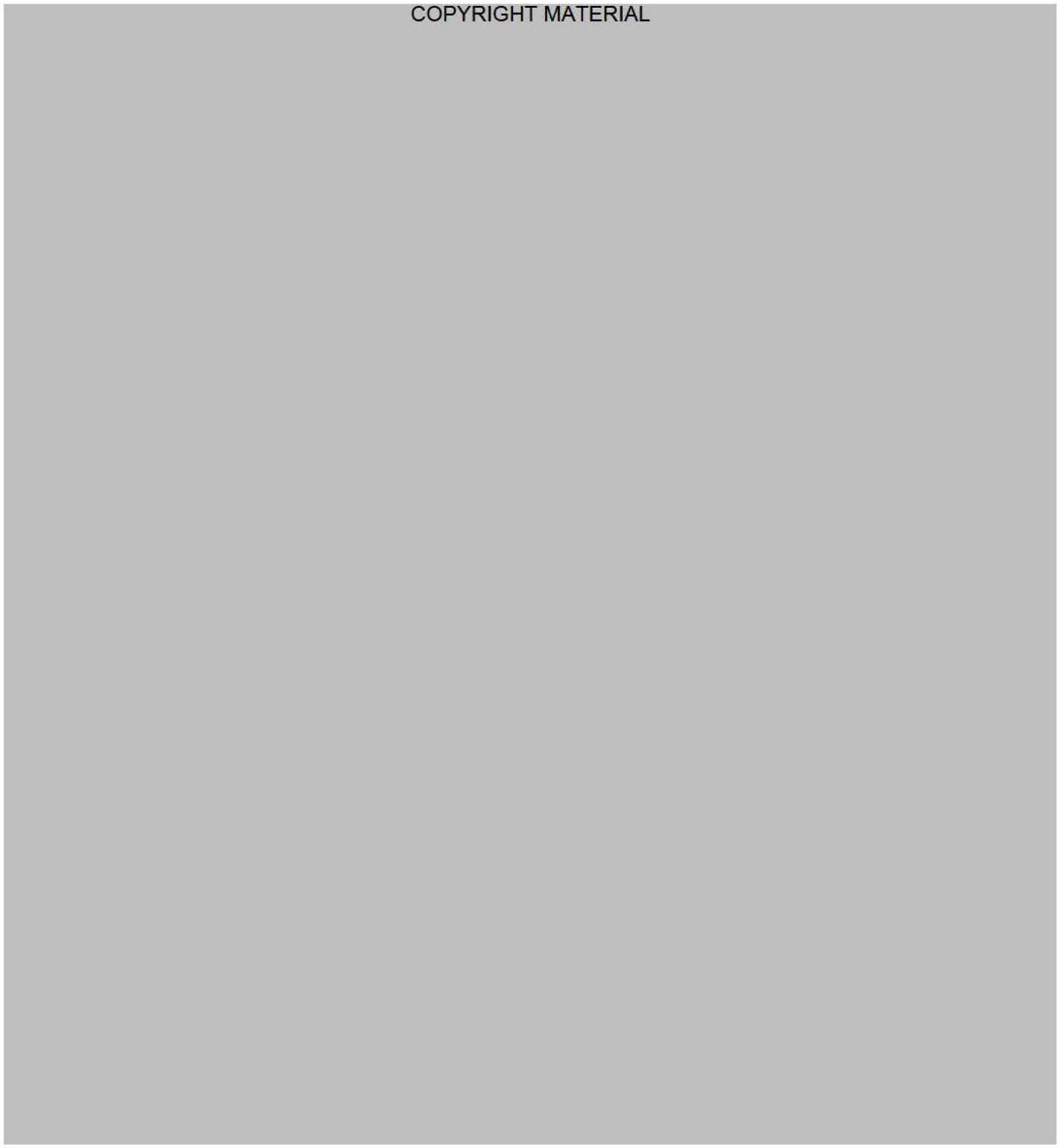
[36] National Toxicology Program 1983, National Toxicology Program Technical Report 247 Carcinogenesis Bioassay of L-Ascorbic Acid (Vitamin C) (CAS No. 50-81-7) in F344/N Rats and B6C3F1 Mice (Feed Study).
[37] Belfield, WO. (1967) Vitamin C in Treatment of Canine And Feline Distemper Complex. Vet Med Small Anim Clin, 62(4), 345-8.
[38] Leveque, J. I. (1969) Ascorbic acid in treatment of the canine distemper complex. Vet Med Small Anim Clin.64(11), 997-9.
[39] Expert Panel, International Journal of Toxicology, 24 (Suppl. 2):51-111, 2005.

Table 8: Ascorbic Acid - Genotoxicity Studies





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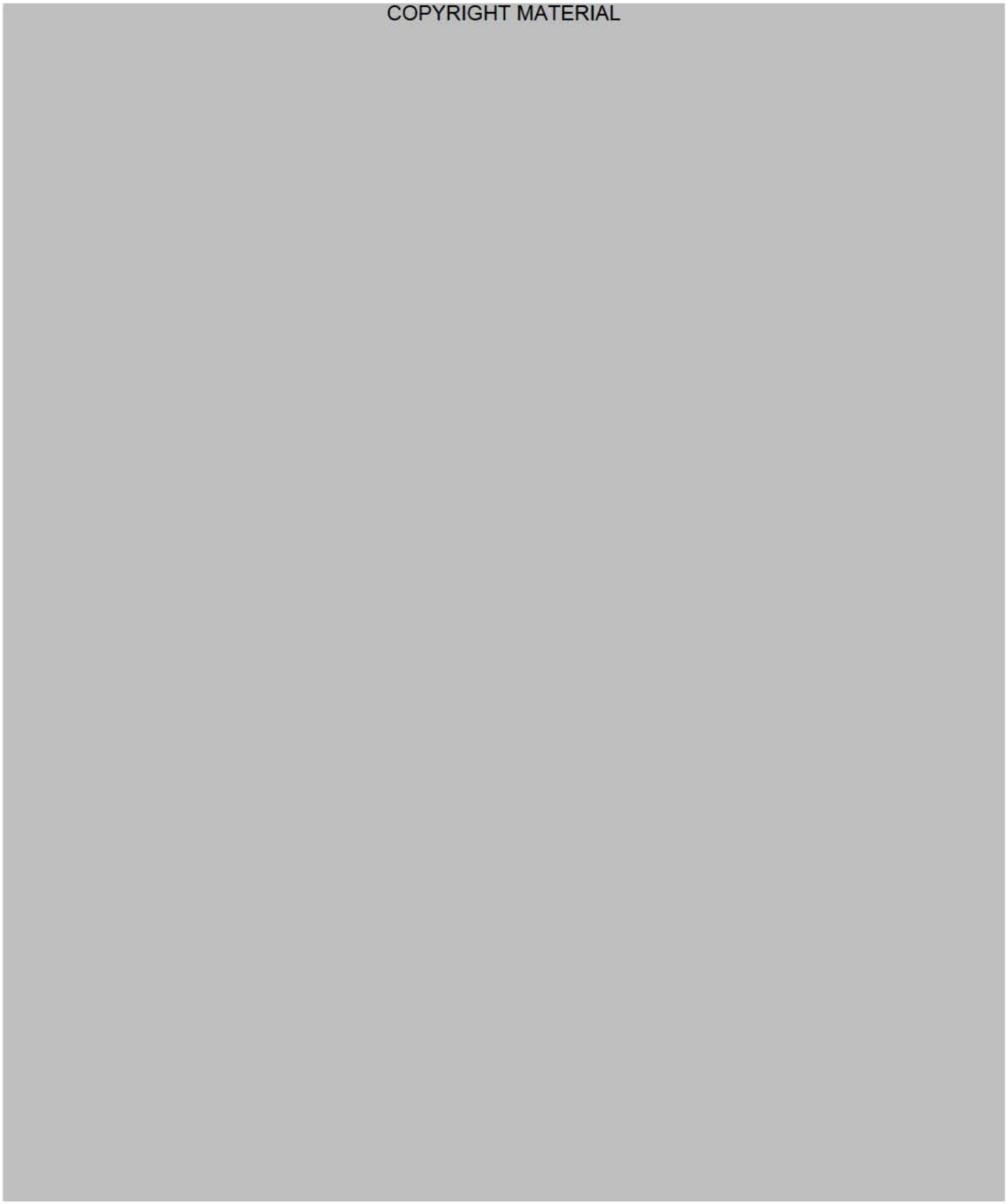
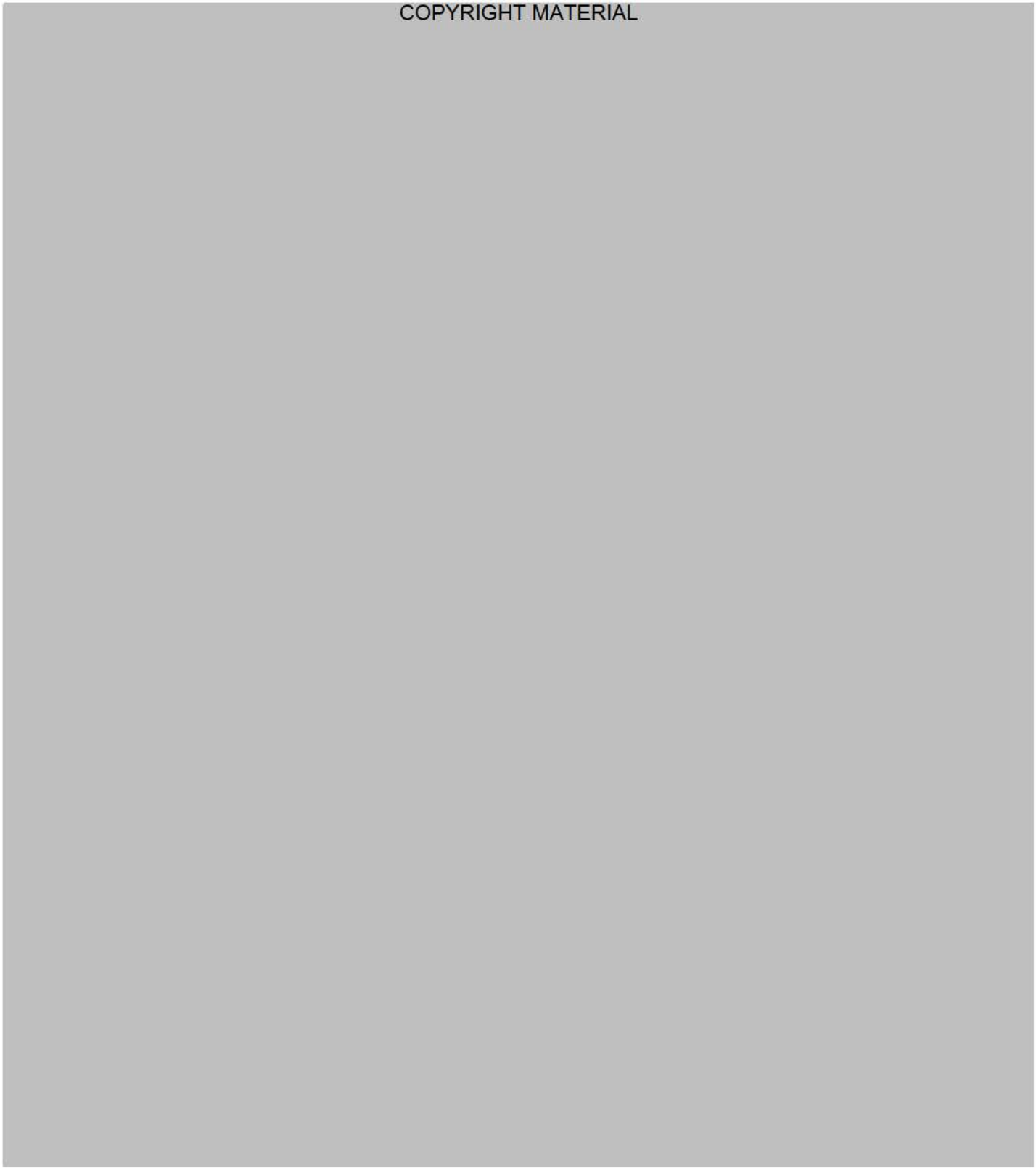
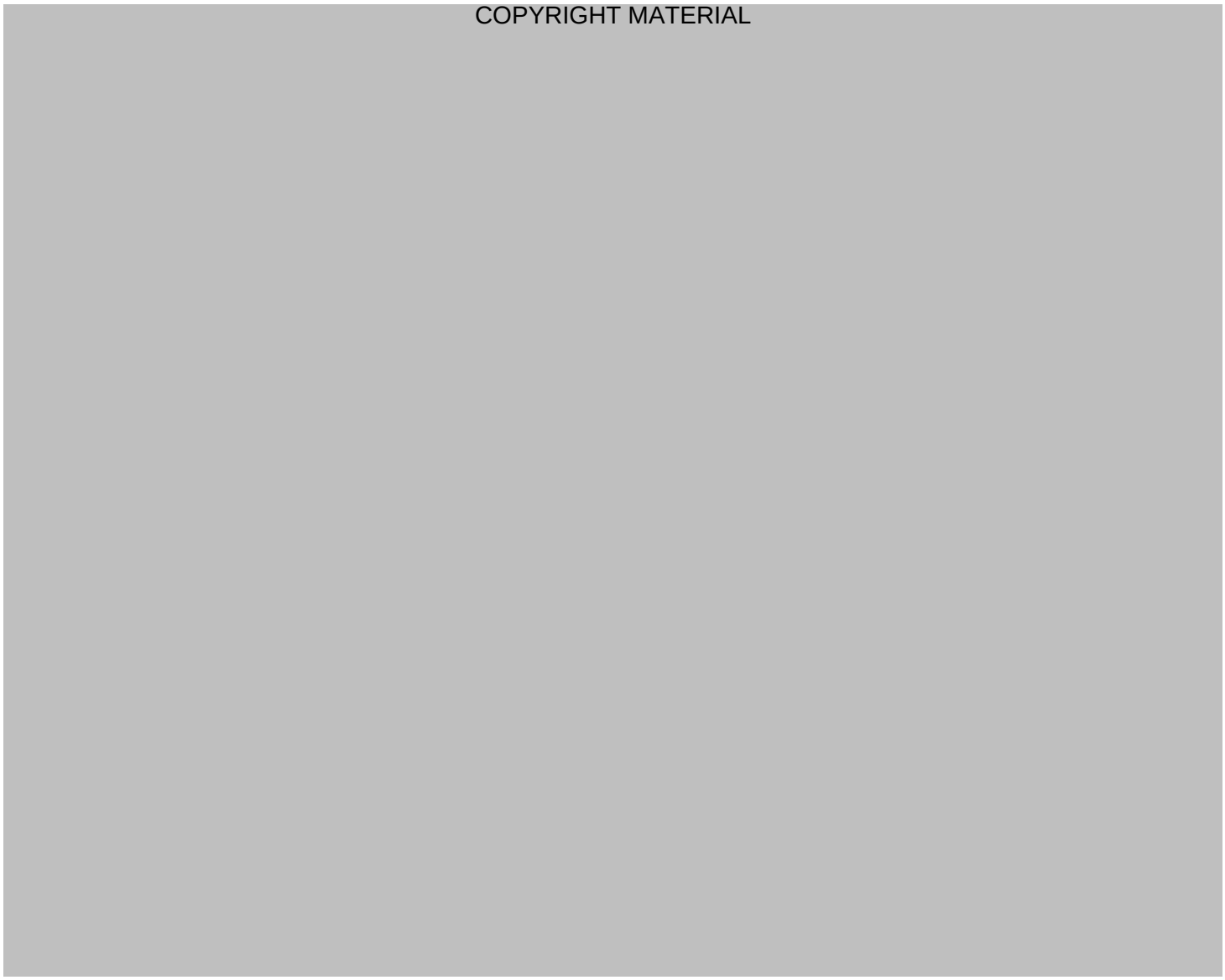



COPYRIGHT MATERIAL



Applicant's table

8 Carcinogenicity

No carcinogenicity studies were conducted by the Applicant.

In general, no data indicate a substantial increase in risk for tumors with a single dose or short-term of dosing of Ascorbic Acid Injection.

The National Toxicology Program (NTP, 1983)[40] investigated the carcinogenic potential of ascorbic acid (at up to 50,000 ppm) in standard 2-year rodent (rats and mice) oral carcinogenicity studies. Findings of these studies suggested that ascorbic acid was not carcinogenic in either species. Findings from another 2 years study with ascorbic acid

[40] *National Toxicology Program 1983 National Toxicology Program Technical Report 247 Carcinogenesis Bioassay of L-Ascorbic Acid (Vitamin C) (CAS No. 50-81-7) in F344/N Rats and B6C3F1 Mice (Feed Study).*

with daily diet doses up to 2,000 mg/kg in rats also suggested ascorbic acid has no carcinogenic potential [41].

Studies related to the carcinogenicity potential of ascorbic acid are summarized in the Table below:

Table 9: Ascorbic Acid - Carcinogenicity Studies

Species	Dose	Route of Administration	Duration	Tumor Findings
Mice/Rats	0-50,000 ppm	Oral	2 years	Negative
Rats	0-2000 mg/kg	Oral	2 years	Negative

9 Reproductive and Developmental Toxicology

No reproductive studies were conducted by the Applicant.

Ascorbic acid has been tested *in vivo* for its potential reproductive effects at up to 1000 mg/kg and *in vitro*. Findings of these studies suggested that ascorbic acid has no adverse reproductive effects at doses relevant to proposed Ascorbic Acid Injection doses.

Table below present submitted references related to reproductive and development toxicity studies with ascorbic acid:

Table 10: Ascorbic Acid - Reproductive Toxicity Studies

Species	Dose (mg/kg/day); Route of Administration	Timing	Findings	Reference
Rats	150, 250, 500, 1000 mg/kg; oral	Day 0 (pre-conception) to 21 Days post-partum and Day 6 to Day 15 of pregnancy	No indications of maternal toxicity, terata, or fetal toxicity: no apparent effect on emborynic or postpartum development, breeding behavior, pregnancy, parturition, or lactation capacity	Frohberg 1973
Mice	150, 250, 500, 1000 mg/kg; oral	Day 6 to Day 15 of pregnancy	No indications of maternal toxicity, terata, or fetal toxicity: no apparent effect on emborynic or postpartum development, breeding behavior, pregnancy, parturition, or lactation capacity	Frohberg 1973

[41] *Surber, W. & Cerioli, A. (1971) A two-year toxicity study with L-ascorbic acid on the rats. Unpublished report of the Battelle Laboratories submitted by Hoffman-La Roche AG.*

Mice	520mg/kg; not specified	Administered for 10 consecutive days during pregnancy	No clear effect on nidation or maternal or fetal survival. Abnormalities in soft and skeletal tissues of treated group similar to control group.	FDRL 1975a
Rats	550mg/kg; not specified	Administered for 10 consecutive days during pregnancy	No clear effect on nidation or maternal or fetal survival. Abnormalities in soft and skeletal tissues of treated group similar to control group	FDRL 1975b
Rats	0, 50, 150 or 450 mg/day; orally	Days 1 to 19 of pregnancy	No increases in abortion or mortality of offspring observed.	Alleva 1976
Hamsters	0, 50, 150 or 450 mg/day; orally	Days 1-15 of pregnancy	No increases in abortion or mortality of offspring observed; slight increase in pup weight observed	Alleva 1976
Mice	3200 mg/kg/day; oral intubation	Days 8-12 of pregnancy	99% survival rate of pups; no teratogenic effects observed; 2 pregnant mice died	Seidenberg 1986
Mice	3.43 or 6.68g/kg, IP	11th day post-copulation; embryos examined day 18-post copulation	6.68g/kg induced 46% increase in fetal death; weight similar to controls and all morphologically normal at both doses. Lower dose (3.4g/kg) ascorbic acid showed no change in fetal mortality; protective against CP-induced toxicity.	Pillans 1990
Rats	100mg/100g body weight; orally	2 weeks prior to and during mating, during pregnancy, and during lactation	No significant effect on body weight of adults, on pregnancy or growth of the litters, the average number of pups born per litter and body weight of the pups.	Nandi 1973
Guinea Pigs	400mg/kg/day Na Ascorbate (twice daily prior to pregnancy for 6 days); SC; ascorbic acid: 0, 50, 150 or 450 mg/day; orally, thereafter	Prior to (Na Ascorbate) and during pregnancy (ascorbic acid)	No increases in abortion or mortality of offspring observed; slight increase in pup weight observed	Alleva 1976

11 Integrated Summary and Safety Evaluation

The Applicant seeks approval for Ascorbic Acid Injection for the treatment of scurvy. Ascorbic acid (also known as vitamin C) is an essential nutrient synthesized by many animals, but not by man because of the absence of the enzyme L-gulonolactone oxidase.

Insufficient dietary intake of ascorbic acid causes scurvy, which is described by symptoms of fatigue, anorexia, muscular weakness, increased susceptibility to infection, and widespread connective tissue weakness, capillary fragility, and death in severe cases [42].

Ascorbic acid is found in food and in dietary supplements and has many biochemical functions in the body, including: the biosynthesis of collagen, L-carnitine, neurotransmitters (e.g., norepinephrine and epinephrine) and protein metabolism [43, 44].

Oral ascorbic acid absorption and distribution in tissues is regulated by active transport and simple diffusion from the gastrointestinal (an inverse dose-dependent, saturation state at up to 50–100 µmol/L). Therefore, oral doses greater than 1 g are absorbed less than 50% [45, 46]. However, the IV administration dose of ascorbic acid is distributed directly in tissues and it's plasma concentration can reach at up to 20 mmol/L with doses of 200 g (100 fold higher compared to oral administration) [47, 48]. Consequently, IV doses of ascorbic acid were investigated in many clinical studies for treatment of various diseases.

Ascorbic acid has been recognized as a GRAS ingredient in food, a dietary supplement, and a component of FDA approved drug products such as multivitamin injection drugs [Infuvite Adult for injection (NDAs 021163) and for infusion (NDA 021559); and Infuvite Pediatric for injection (021265) and for infusion (NDA 021646)].

The recommended daily allowances of ascorbic acid in the United States are listed below:

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[42] Anderson, L. C., Otto, G., Pritchett-Corning, K. R., Whary, M. T. (2015). Laboratory Animal Medicine, 3rd Edition: Elsevier.
[43] Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr 2007;137:2171-84.
[44] Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 1999;69:1086-107.
[45] Graumlich JF, Ludden TM, Conry-Cantilena C, Cantilena LR, Jr, Wang Y, Levine M. Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. Pharm Res 1997; 14:1133–1139.
[46] Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996; 93:3704–3709.
[47] Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004; 140:533–537.
[48] Verrax J, Calderon PB. The controversial place of vitamin C in cancer treatment. Biochem Pharmacol 2008; 76:1644–1652.

Age	Male	Female	Pregnancy	Lactation
0–6 months	40 mg*	40 mg*		
7–12 months	50 mg*	50 mg*		
1–3 years	15 mg	15 mg		
4–8 years	25 mg	25 mg		
9–13 years	45 mg	45 mg		
14–18 years	75 mg	65 mg	80 mg	115 mg
19+ years	90 mg	75 mg	85 mg	120 mg
Smokers	Individuals who smoke require 35 mg/day more vitamin C than nonsmokers.			

** Adequate Intake (AI)*

NIH - Office of Dietary Supplements - Updated: February 11, 2016

In addition, 200 mg/day of ascorbic acid is recommended for those need daily parenteral multivitamin supplementation. A tolerable upper intake level of ascorbic acid was established by the Food and Nutrition Board of the National Academy of Sciences (2000) as 2 g/day based on reports of diarrhea and other gastrointestinal disturbances at intakes of greater than 3 g/day from clinical studies. However, in clinical studies, much higher dosages of Ascorbic Acid Injection (up to 100 g/day) were used to investigate ascorbic acid's potential as antibacterial, anticancer, recovery injury/surgery, and disease-related fatigue [49, 50].

The proposed MHRD(s) are the following: from (b) (4) To support these doses, no animal studies were conducted. The Applicant instead relies on the available nonclinical data to support the marketing application for Ascorbic Acid Injection.

Ascorbic acid has been tested in rodent and non-rodents by both parenteral and oral routes of administration in studies of ranging from acute to chronic studies to two year durations for carcinogenicity at doses up to 2500 mg/kg. Based on a chronic feeding rats study, Cosmetic Ingredient Review Expert Panel Report (1965) stated that ascorbic acid at 25 mg/kg bw showed no treatment-related toxicity. Results of genetic toxicity studies with ascorbic acid suggested that ascorbic acid is not genotoxic. National Toxicology Program (NTP) investigated the potential of carcinogenicity of ascorbic acid (at up to 50,000 ppm) in the 2-year standard rodent (rats and mice) oral carcinogenesis

[49] *Fritz H, Flower G, Weeks L, Cooley K, Callachan M, McGowan J, et al. Intravenous vitamin C and cancer: a systematic review. Integr Cancer Ther 2014; 13:280–300.*
[50] *Lee WJ. The prospects of vitamin C in cancer therapy. Immune Netw 2009; 9:147–152.*

studies. Findings of these studies suggested that ascorbic acid was not carcinogenic in either species. Results from another 2 years study with ascorbic acid with daily dietary doses up to 2,000 mg/kg in rats suggested ascorbic acid has no potential of carcinogenicity [51]. Ascorbic acid has been tested *in vivo* and *in vitro* for its potential reproductive effects at up to 1000 mg/kg. Findings of these studies do not suggest that ascorbic acid has potential to induce reproductive toxicity at the proposed doses. For reproductive toxicities in humans, ascorbic acid at MHRD (b) (4) in adults (b) (4)

The safety margins to the proposed MHRD in adults and children based on IV administration of ascorbic acid in published short-term toxicity studies using different nonclinical species (based on surface area) and findings from rodent carcinogenicity studies by the oral administration of ascorbic acid for two years are summarized in the Table below:

Table 11: Safety Margins† to the Proposed Maximum Recommended Human Dose - Carcinogenicity Findings

Intravenous Studies					
Species	NOAEL	Route	Duration	Safety Margin to MHRD* (Adults)** (b) (4)	Safety Margin to MHRD* (Children)** (b) (4)
Mice	1000 mg/kg	IV	7 Days		
Guinea Pigs	2500 mg/kg	IV	6 days		
Rats	100/100 g	IV	21 days		
Carcinogenicity Studies					
Species	NOAEL	Route	Duration	Safety Margin to MRHD	Tumor Findings
Mice/Rats	50,000 ppm	Oral	2 years	Not calculated ***	Negative
Rats	2000 mg/kg	Oral	2 years	Not calculated ***	Negative

† Safety margins are based on the absence of any ascorbic acid-related toxicity at the maximum recommended human dose (MRHD).
** Based on body surface area extrapolation.*
*** Based on proposed MHRD(s) in adults and children in the following:* (b) (4)

.
**** Carcinogenicity studies were not conducted by the intravenous route; however, vitamin c has high oral bioavailability.*

[51] *Surber, W. & Cerioli, A. (1971) A two-year toxicity study with L-ascorbic acid on the rats. Unpublished report of the Battelle Laboratories submitted by Hoffman-La Roche AG.*

In general, findings from nonclinical studies with ascorbic acid in different species with varying routes of administrations in both acute and chronic studies up to 2500 mg/kg (body weight) and for up to 2 years duration suggest no toxic effects at doses greater than the proposed maximum human recommended dose (MHRD) in adults and children, with adequate safety margins.

In clinical studies, overdose symptoms of Ascorbic Acid Injection were reported mostly with temporary faintness or dizziness [52]. A few cases were reported with hemolytic anemia (due to hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, G6PD) [53]. Moreover, Ascorbic Acid Injection up to 200 g for treatment of infection and/or cancer, were reported with side effects in 1% of patients (101/9328) including minor fatigue, change in mental status and two deaths related to renal impairment and G6PD [54].

Previously, injection of ascorbic acid for treating and preventing low levels of vitamin C had been used in the U.S. market for two products of Cenolate (since 1938) and Ascor L 500 (since 2002). Both drugs withdraw voluntarily in 2010 to comply with FDA's Unapproved Drug Initiative. Cenolate and Ascor L 500 had similar intravenous dosages for adult and pediatric as following: adult: 50 to 200 mg/day for dietary supplement; 4 to 12 g/day in 3 to 4 divided doses for urinary acidification; 100 to 250 mg once or twice daily for a minimum of two weeks for scurvy; and pediatric: 35 to 100 mg/day for dietary supplement; 500 mg every 6 to 8 hours for urinary acidification; 100 to 300 mg/day in divided doses for a minimum of two weeks for scurvy.

The major clinical concern with a high dose IV administration of ascorbic acid is the formation of oxalic acid (metabolism of ascorbic acid), which can lead to crystallization (calcium oxalate) in the urinary space (especially in the renally impaired population). Consequently, as noted in the labeling insert, there is a safety risk in patients with renal impairment, on dialysis, or those who have a history of renal calculi with high dose of IV ascorbic acid administration. Also, because ascorbic acid can increase iron absorption, it could cause elevated iron stores in patients with iron overload due to hemochromatosis, thalassemia, major sideroblastic anemia and/or other diseases requiring multiple red blood cell transfusions. Moreover, ascorbic acid consumption was reported with hemolysis in patients with G6PD after large oral (3 to 4g over 4 to 6 hours) or IV doses (e.g. 40 to 80g). Therefore, IV administration of high dose ascorbic acid should be carefully considered in patients with chronic kidney disease, G6PD, and iron overload.

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[52] Sestili MA: Possible adverse health effects of vitamin C and ascorbic acid. Semin Oncol. 1983;10:299.
[53] Campbell GD, Steinberg MH, Bower JD. Ascorbic acid-induced hemolysis in G-6-PD deficiency. Ann Int Med 1975;82(6):810. Letter.
[54] Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010; 5:e11414.

There are no safety concerns in the existing nonclinical database at the proposed doses of Ascorbic Acid Injection in children and adults that would require additional nonclinical studies to be conducted.

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/s/

PARVANEH ESPANDIARI
08/28/2017

CALVIN L ELMORE
08/29/2017
I concur with the recommendation for approval.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 209112	Applicant: McGuff Pharmaceuticals, Inc.	Stamp Date: 9/2/2016
Drug Name: Ascorbic Acid Injection	NDA Type: 505(b)(2)	Indication: Treatment of scurvy

Regulatory History: Ascorbic Acid Injection (500mg/mL) is being developed by McGuff Pharmaceuticals for the treatment of scurvy.
To support the use of Ascorbic Acid Injection, no animal studies were conducted; however, the Applicant submitted published available information.
In general, Ascorbic Acid has been recognized as a GRAS ingredient in food, as a dietary supplement and as an Active Pharmaceutical Ingredient (API) and component in FDA approved drug products such as multivitamin injection drugs. Also, Ascorbic Acid Injection, USP has been marketed in the US since 1938 (Cenolate, adult dose for Scurvy with oral, IM, IV, SC: 100 to 250 mg once or twice daily for a minimum of two weeks). In addition, the Sponsor's formulation (Ascor L 500®; Ascorbic Acid Injection, USP) was marketed in the United States from 2002 through December 2010 until it was voluntarily withdrawn to comply with FDA's Unapproved Drug Initiative. Moreover, Ascor L 500® currently is marketed as an approved drug product in Canada and New Zealand with dosing up to 2 grams daily without evidence of toxicity.

On **initial** overview of the NDA application for filing: The NDA appears fileable from a Pharm/Tox point of view.

	Content Parameter	Yes	No	Comment
	s the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The eCTD submission has 5 modules – regional (forms) for common technical document summary, quality (CMC), nonclinical study reports (pharm/tox), and clinical study reports (clinical trials).
2	s the pharmacology/toxicology section ndexed and paginated in a manner allowing substantive review to begin?	X		
3	s the pharmacology/toxicology section egible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 ncluding referenced literature) completed and submitted carcinogenicity, mutagenicity, teratogenicity, effects on fertility, uvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No non-clinical studies were conducted. For supporting nonclinical safety, published literature was submitted. Carcinogenicity studies have not been conducted with Ascorbic acid injection.
5	f the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by			n/a. No nonclinical studies were conducted.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
	the appropriate route been conducted ith appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			n/a. No nonclinical studies were conducted.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed n accordance with the GLP regulations 21 CFR 58) or an explanation for any significant deviations?			n/a. No nonclinical studies were conducted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and n accordance with 201.57?			n/a. No nonclinical studies were conducted.
0	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		All impurities were within ICH qualification threshold for the drug substance.
1	Has the applicant addressed any abuse potential issues in the submission?			n/a.
2	f this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

There are no potential review issues to be forwarded to the Applicant for the 74-day letter.

Below statements are from PIND (076483) pre meeting minutes regarding the discussion between the Applicant and the Agency related to non-clinical studies to support the safety of Ascorbic Acid Injection:

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

"PreClinical

No Preclinical studies have been conducted by MPI. McGuff Pharmaceuticals believes that product safety is assured by the historical use of the product, the GRAS status of Ascorbic Acid, USP and the use of excipients that meet all USP compendial standards (See References- Appendix 4 and Appendix 5)

- *Does the Agency agree that a waiver for the requirements of safety is acceptable? Is this waiver included in the application or obtained before submission?*

FDA RESPONSE:

No, the sponsor needs to provide safety data supporting their product. This may include literature or other publicly available information. Demonstration of comparability to the oral product experience may be useful to demonstrate safety. Data may be needed to qualify any impurities or residual solvents in the drug product in accordance with ICH Q3."

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/s/

PARVANEH ESPANDIARI
10/13/2016

CALVIN L ELMORE
10/13/2016