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Bioequivalence of coenzyme Q_{10} from over-the-counter supplements

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Abstract

The objective of this study was to compare the relative bioavailability of two new products with solubilized and non-solubilized over-the-counter (OTC) coenzyme Q_{10} products. Nine healthy adults were given single 180 mg doses of each coenzyme Q_{10} formulation at two week intervals. A commercially-marketed, non-solubilized Q_{10} powder formulation (product D) was only minimally absorbed, and was excluded from the analysis of data. ANOVA comparison of maximum plasma concentrations (C_{max}), time of maximum concentrations (t_{max}), areas under the concentration-time curves from times zero to 144 hours post dose (AUC_{0-144h}), and areas under the concentration-time curves from times zero to infinity ($AUC_{0-\infty}$) were not significantly different ($P > 0.05$) between test products A (LiQ-10™) and B (Q-Nol™) and the reference product C (UbiQGel®). The upper limits of the 90% confidence intervals of the log-transformed ratios (A:C and B:C) of $C_{max,}$ $AUC_{0-144h,}$ and $AUC_{0-\infty}$ were >1.25 for both test products, but significant ($P < 0.05$) only for the B:C $AUC_{0-144h.}$ The results of this study indicate that LiQ-10™ has increased bioequivalence compared to the reference product, but did not reach statistical significance. Q-Nol™ has increased bioavailability compared to the reference product ($P < 0.05$). © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Coenzyme $Q_{10;}$ Ubiquinone; Ubiquinol; Ubidecarenone; Bioequivalence; Bioavailability

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1. Introduction

Coenzyme Q_{10} (ubiquinone or ubidecarenone) is an endogenous enzyme cofactor that is produced in all living cells in humans. Coenzyme Q_{10} functions to promote the proton/electron translocation in mitochondria and lysosomes [1,2], protects mitochondria from free radical damage [3,4], may play a role in the permeability transition of the inner mitochondrial membrane [5], and is thought to be capable of preventing programmed cell death or apoptosis [6]. Recently interest in coenzyme Q_{10} has increased because of evidence that it may function together with α-tocopherol in protecting the function of biological membranes [7], recycling α-tocopherol by sparing or regeneration [8], preventing the prooxidant effects of α-tocopherol [9], and providing lipoprotein with increased resistance to oxidation [9,10].

Coenzyme Q_{10}, which is marketed in the USA as an over-the-counter (OTC) dietary supplement, is a useful therapeutic agent for certain conditions associated with increased oxidative stress. In a recent review, Mongthuong and colleagues concluded that coenzyme Q_{10} may be recommended as adjuvant therapy for chronic heart failure [11]. Preliminary studies suggest benefits from coenzyme Q_{10} supplementation following cardiac surgery [12,13], in patients with chronic renal failure [14], and in patients with mitochondrial cytopathies [15–17]. A large, multicenter, randomized placebo-controlled trial recently reported benefits from coenzyme Q_{10} supplementation in patients with Huntington's disease [18].

The absolute bioavailability of coenzyme Q_{10} is unknown. Coenzyme Q_{10} is strongly lipophilic, practically insoluble in aqueous solution, and has poor bioavailability in humans. The importance of product formulation was recognized early in the development of coenzyme Q_{10} preparations [19]. Studies which attempted to improve coenzyme Q_{10} bioavailability with emulsifying agents and oil-based vehicles had limited success improving bioavailability [20–21]. A fully-solubilized coenzyme Q_{10} formulation was compared with two other preparations, and found to provide a 2.5 to three-fold increase in bioavailability [22]. The fully-solubilized product in that study was selected as the reference product for the current study (product C), because it appears to have the highest bioavailability of currently marketed Q_{10} OTC products.

The purpose of this study was to compare the relative bioavailability (or bioequivalence) of four coenzyme Q_{10} formulations. Specifically, the relative bioequivalence of two newly developed formulations, i.e. a liquid containing solubilized coenzyme Q_{10} (product A or LiQ-10^{TM}) and a soft capsule containing ubiquinol (the reduced form of coenzyme Q_{10}) (product B or Q-Nol^{TM}), are compared with two marketed OTC products, i.e. one containing fully-solubilized coenzyme Q_{10} (product C or UbiQGel$^{®}$) in the oxidized form (ubiquinone) and the other a commercial hard capsule product (product D) containing non-solubilized Q_{10} powder. The secondary aim of this study was to compare subject tolerance of these coenzyme Q_{10} products.

2. Materials and methods

2.1. Subjects

This study was approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA. Written informed consent was obtained

from all subjects. Thirteen healthy adult volunteers were enrolled into this study. The results of routine laboratory tests, including complete blood count, chemistry profile, lipid profile, and urinalysis, were within the normal ranges. Volunteers had no histories of diseases which might affect coenzyme Q_{10} absorption. No subjects were taking supplements of coenzyme Q_{10} for at least four weeks prior to the study, or other vitamin supplements for at least two weeks prior to the study. None had taken an investigational drug for at least one month before this study.

2.2. Study design

The first phase of this study was a run-in period in which a 180 mg dose of product D, a commercial product containing non-solubilized coenzyme Q_{10} powder in a hard capsule (30 mg/capsule), was administered to each subject. A previous study reported that granular, non-solubilized coenzyme Q_{10} was minimally absorbed in adults following a single dose [21]. Product D was tested to rule out the possibility of aberrant coenzyme Q_{10} absorption by any subject, and to confirm the poor absorption characteristics of non-solubilized coenzyme Q_{10} in a crystalline or powder formulation.

Two weeks following the run-in phase a single dose, randomized, crossover study of three products was conducted at the Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. Test product A, LiQ-10™ (10 mg ubiquinone per mL; Control #0061–0070, Tishcon Corp., Westbury, NY, USA), is a liquid syrup formulation which contains solubilized coenzyme Q_{10} in the oxidized form. Test product B, Q-Nol™ (30 mg per capsule; Control #0041-E-0070, Tishcon Corp., Westbury, NY, USA) is a soft gel capsule formulation containing coenzyme Q_{10} in the reduced form (ubiquinol). Test product C (the control formulation), UbiQGel® (30 mg ubiquinone/capsule; Control #0651–0800, Tishcon Corp., Westbury, NY, USA), is a marketed soft gel capsule containing solubilized coenzyme Q_{10} in the oxidized form. Single 180 mg doses of each formulation were administered in random sequence separated by a two week washout interval. Randomization was determined using a random numbers generator.

Before each study phase all subjects fasted for at least ten hours prior to the coenzyme Q_{10} dose, and continued to fast for the first four hours following each dose. Doses were administered with 240 mL of water at approximately 8:00 AM immediately following collection of a baseline blood sample. Lipid profiles were also tested before each dose to insure the fasting state of each volunteer. Following each coenzyme Q_{10} dose ten blood samples were collected during the subsequent 144 hours (2.0, 4.0, 6.0, 8.0, 10, 12, 24, 48, 96, and 144 hours post dose).

During the first 12 hours of each study phase the subjects remained in the medical center. Two cafeteria-style meals were provided at approximately 12:30 PM and 6:00 PM. Subjects were permitted to leave the medical center after the first 12 hours following each dose, but were required to return at the scheduled times for additional blood sample collection. The remaining blood samples (from 24 hours through 144 hours) were collected between 7:30 AM and 9:00 AM after overnight fasting.

2.3. Sample collection and processing

Blood specimens were collected from the antecubital vein into glass vacuum tubes containing sodium heparin. Blood was immediately refrigerated, then tubes were centrifuged within one hour of collection at 2,000 *g* for ten minutes at +5° C. Plasma was immediately transferred to a pre-labeled, two mL screw-capped polypropylene tubes, then stored at −80° C until analysis.

2.4. Coenzyme Q_{10} analysis

Plasma samples were analyzed for total plasma coenzyme Q_{10} concentrations in the Clinical Neuropharmacology Laboratory of the Cincinnati Children's Hospital Medical Center using a previously validated high performance liquid chromatography (HPLC) procedure with electrochemical detection [23]. In brief this new method measures oxidized, reduced, and total coenzyme Q_{10} concentrations in plasma over an analytical range from 0.01 to 4.0 mg/L. The intra-assay and inter-assay CVs were 1.2–4.9% across this concentration range. This optimized method provides reliable determination of coenzyme Q_{10} in plasma.

All other tests (chemistry profiles, complete blood counts, lipid profiles, and urinalysis) were provided by the Clinical Laboratory Service of the Cincinnati Children's Hospital Medical Center.

2.5. Pharmacokinetics analysis

The pharmacokinetics of each coenzyme Q_{10} product was determined by the noncompartmental method. Following each dose the increase in plasma concentration above the predose endogenous coenzyme Q_{10} concentration was used to calculate pharmacokinetic parameters. Maximum plasma coenzyme Q_{10} concentration (C_{max}), time of maximum concentration (t_{max}), and area-under-the-concentration curve (AUC_{0-144h} and $AUC_{0-\infty}$) were determined using WinNonlin™ software (version 1.5, Pharsight Corp., Mountain View, CA, USA).

2.6. Statistical analysis

All of the response variables were transformed to the (natural) logarithmic scale. Two-way mixed model Analyses of Variance were conducted on each of the response variables C_{max}, AUC_{0-144h}, $AUC_{0-\infty}$, and the concentrations at the each of the eleven time points (baseline and ten post treatment). The two factors were product (fixed effect) and subject (random effect). The period and sequence factors were ignored for this part of the analysis.

A mixed model procedure (SAS® PROC MIXED, SAS Institute Inc., Cary, NC, USA) was used for assessing bioequivalence in this crossover design study [24]. This procedure provides for the direct calculation of the Schuirmann 90% confidence intervals [24]. Bioequivalence was established if the 90% confidence interval of this difference, back-transformed using exponentiation, was contained in the interval (0.8, 1.25).

2.7. Safety assessments

Following each coenzyme Q_{10} dose subjects were required to record whether or not they had experienced any untoward effects. A standard form was completed and signed by each subject to document whether or not ill effects were noted.

3. Results

3.1. Subject demographics and discontinuations

Nine subjects (eight M/one F), ranging in age from 23 to 56 y (median 36 y) and weighing 55 kg to 103 kg (median 87 kg), completed all four phases of the study. The weight-adjusted median dose of coenzyme Q_{10} administered was 2.1 mg/kg (range 1.8 to 3.3 mg/kg).

Thirteen subjects were enrolled into this study. Three subjects failed to complete the study for personal reasons unrelated to the study products. A fourth individual was considered to be noncompliant with the study protocol because of intermittently high triacylglycerol ($>$ 400 mg/dL) and total cholesterol ($>$ 250 mg/dL) concentrations. Data from these four subjects were excluded from the analysis. All other chemistry, blood, and lipid profile results were within the normal range for healthy adults.

3.2. Bioequivalence comparisons

Comparison of predose coenzyme Q_{10} concentrations during each study phase indicated that plasma concentrations had returned to baseline (endogenous) concentrations, and there was no indication of carryover effect from the previous dose (Fig. 1). The absorption curve following administration of the non-solubilized powder formulation (product D) confirmed that all subjects had minimal absorption of coenzyme Q_{10} (Fig. 2). Five of nine subjects had a maximum coenzyme Q_{10} concentration (C_{max}) $\leq$ 0.1 μg/mL above baseline (predose) concentration. Only one individual had a $C_{max} > 0.2$ μg/mL above the baseline concentration, i.e. 0.23 μg/mL, following the dose of non-solubilized coenzyme $Q_{10.}$ These data, which confirmed previous findings [21], were excluded from the final bioequivalence analysis.

Significantly increased coenzyme Q_{10} concentrations (greater than the reference product C) occurred for product B at C_{2h} (0.158 μg/mL, $P = .018$), C_{8h} (0.163 μg/mL, $P = .047$), C_{10h} (0.133 μg/mL, $P = .023$), C_{12h} (0.144 μg/mL, $P = .026$) (Fig. 2). Coenzyme Q_{10} concentrations following the dose of product A were significantly increased at C_{10h} (0.157 μg/mL, $P = .009$) and C_{12h} (0.140 μg/mL, $P = .029$) (Fig. 2). It should be noted, however, that if the nominal level of .05 is adjusted for the 30 paired comparisons, using a Bonferroni correction, then none of the above differences is significant at an experiment-wise error rate equal to .05.

The t_{max} values for products A, B, and C were very consistent. All subjects, except two for product A, one for product B, and one for product C, had t_{max} occur six hours after each coenzyme Q_{10} dose (Table 1). The mean C_{max} of product A is similar to product C, but

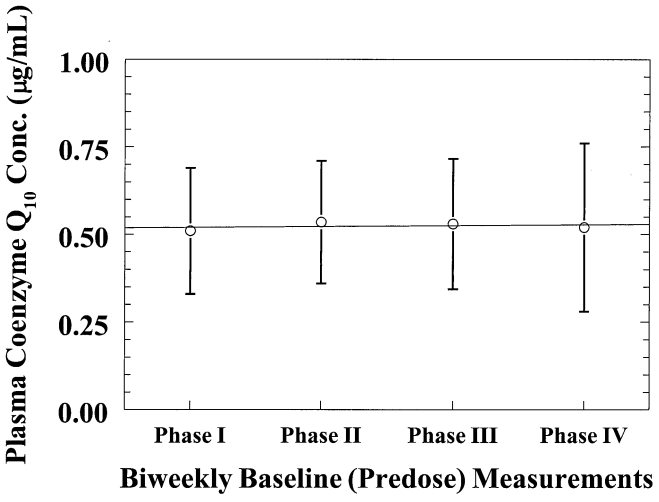

Fig. 1. Comparison of mean (SD) coenzyme Q_{10} plasma concentrations prior to the administration of coenzyme Q_{10} test doses during the run-in period (phase I) and each study phase (phases II-IV). No significant difference exists between these concentrations. The regression line is provided to show the constancy of baseline (endogenous) coenzyme Q_{10} plasma concentrations throughout the study.

product B is approximately 25% higher than product C (Tables 1 and 2). This difference did not reach statistically significance, however, probably due to the limited number of subjects. The upper limits of the 90% confidence intervals of the log-transformed ratios of C_{max}, AUC_{0-144h}, and $AUC_{0-\infty}$ for products A and B were >1.25, although statistical significance is reached only for AUC_{0-144h} of product B ($P < 0.05$) (Table 2). The 90% confidence interval of C_{12h} is also significantly increased for product B ($P < 0.05$) (Table 2).

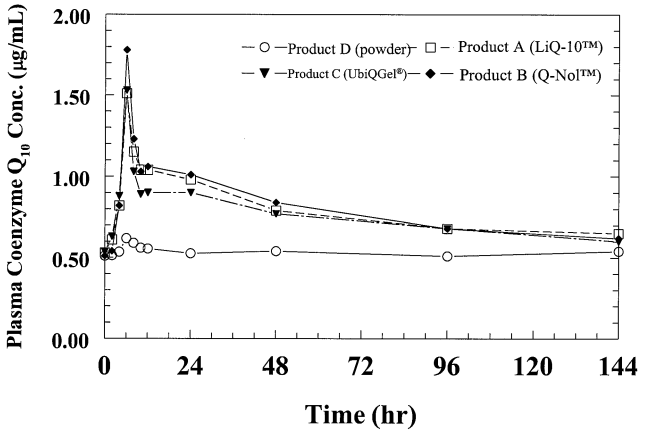

Fig. 2. Comparison of mean (SD) coenzyme Q_{10} plasma concentrations just prior to and following each coenzyme Q_{10} study dose. Coenzyme Q_{10} concentrations following administration of the non-solubilized powder formulation (product D) were not included in the statistical analysis to the other products, because of the minimal change from baseline which occurred following administration.

Table 1
Changes in pharmacokinetic parameters (mean ± SD) of coenzyme Q_{10} measured above baseline concentrations following administration of single 180 mg doses of four coenzyme Q_{10} products to nine healthy adults

Product	C_{max} (mg L^{-1})	t_{max} (h)	C_{12h} (mg L^{-1})	AUC_{0-144h} (mg · h L^{-1})	$AUC_{0-\infty}$ (mg · h L^{-1})
A (LiQ-10™)	1.03 ± 0.37	6.2 ± 1.6	0.51 ± 0.13[a]	35.82 ± 14.15	51.67 ± 38.01
B (Q-Nol™)	1.27 ± 0.66	8.1 ± 6.3	0.55 ± 0.19[a]	41.09 ± 21.82	55.26 ± 34.53
C (UbiQGel®)	1.03 ± 0.50	5.8 ± 0.7	0.37 ± 0.06	30.0 ± 9.33	38.80 ± 17.33
D (Q_{10} powder)	0.12 ± (0.05)	6.7 ± 1.0	0.05 ± 0.06	2.81 ± 3.46	—

[a] C_{12h} for product A and product B compared with C_{12h} for reference product C ($P < 0.05$).

3.3. Safety

No significant adverse effects were reported during this study. Two subjects reported mild stomach discomfort approximately 30 minutes after the coenzyme Q_{10} dose, each of which lasted less than 1 hour. One of these two subjects experienced mild gastric discomfort on two separate occasions, once following the liquid formulation (product A) and again following the reduced coenzyme Q_{10} formulation (product B). The other individual experienced gastric discomfort only after taking the liquid formulation (product A). No additional treatment was required for either of these subjects, and both individuals completed all four phases of the study.

4. Discussion

The safety profile of coenzyme Q_{10} appears to be quite good. Mild gastrointestinal disturbances have been reported by other studies, but rarely required discontinuation of coenzyme Q_{10} supplementation. All subjects who participated in this study tolerated 180 mg

Table 2
Statistical analysis of bioequivalence of log-transformed C_{max}, C_{12h}, AUC_{0-144h}, and $AUC_{0-\infty h}$ of two coenzyme Q_{10} products (A or LiQ-10™, B or Q-Nol™) vs. control (reference) product C (UbiQGel®) after administration of 180 mg as single doses to nine healthy adults

Test vs. control	C_{max}		C_{12h}		AUC_{0-144h}		$AUC_{0-\infty}$	
	A vs. C	B vs. C	A vs. C	B vs. C	A vs. C	B vs. C	A vs. C	B vs. C
Geometric mean ratio (test/control)	1.06	1.24	1.15	1.16	1.14	1.27	1.18	1.32
Range (arithmetic ratios)	0.42–2.38	0.77–2.36	1.94–3.13	2.56–5.64	0.88–2.07	0.89–1.28	0.91–1.32	0.77–1.41
90% Confidence Interval	0.82–1.36	0.96–1.61	1.02–1.27	1.03–1.29*	0.89–1.34	1.05–1.59*	0.81–1.59	0.99–1.95

* $P < 0.05$

doses of coenzyme Q_{10} very well, even though all doses were taken after an overnight fast with 240 mL of water.

Although the safety profile of coenzyme Q_{10} appears to be good at lower doses (<100 mg/day), adverse effects have been associated with higher doses. One report suggested that treatment with coenzyme Q_{10} prior to intense exercise caused increased plasma creatine kinase and cellular damage [25]. However, other reports involving coenzyme Q_{10} supplementation in endurance trained athletes and untrained men do not support these findings [26–28]. One placebo-controlled, double blinded trial evaluated the effects of coenzyme Q_{10} and α-tocopherol supplementation before and after running a marathon [29]. The increase in baseline creatine kinase was somewhat less in the coenzyme Q_{10} supplemented group than in the placebo group [29].

Larger doses of coenzyme $Q_{10,}$ from 200 mg/day to 1,200 mg/day, have been administered chronically to patients without significant adverse events [18,30–32]. Langsjoen and colleagues reported that coenzyme Q_{10} dosing (mean 242 mg/day, range 75 mg/day to 600 mg/day) by 424 cardiovascular disease patients caused no apparent side effects, except for one individual who experienced nausea [30]. Feigin and colleagues studied the effects of high dose (600 mg/day to 1,200 mg/day) coenzyme Q_{10} in 10 patients with Huntington's Disease [31]. Two individuals experienced heartburn and headache, which were graded as mild to moderate severity [31]. None of the adverse events required reduction or discontinuation of coenzyme Q_{10} [31]. Shults and colleagues studied the tolerability of coenzyme Q_{10} in 15 patients with Parkinson's Disease [32]. Dosages of coenzyme Q_{10} ranged from 400 mg/day to 800 mg/day [32]. None of the patients reported adverse effects [32]. Two patients, taking 800 mg/day, were observed to have three to five hyaline casts per low power field and trace protein on repeat urinalysis [32]. No abnormalities were noted on follow-up after discontinuation of coenzyme Q_{10} [32]. These authors recommend prudent monitoring of renal function with coenzyme Q_{10} dosing greater than 600 mg/day [32]. In addition, taking coenzyme Q_{10} with food seems to be advisable for individuals who are sensitive to the gastrointestinal effects, although it should be noted that the effect of food on coenzyme Q_{10} absorption has not been clearly delineated.

Assessment of coenzyme Q_{10} bioequivalence must take into account endogenous concentrations of this substance. Endogenous concentrations of coenzyme Q_{10} in plasma are relatively stable over time. In the current study predose coenzyme Q_{10} concentrations were unchanged during the study (Fig. 1). In addition the stability of endogenous coenzyme Q_{10} concentrations can be observed between 24 hours and 144 hours following administration of product D, which was minimally absorbed (Fig. 2).

It has been reported that the average dietary intake of coenzyme Q_{10} in Denmark is only three to five mg per day [33]. A variety of food items were tested for coenzyme Q_{10} content, and it was found that certain meats, i.e. pork, poultry, and beef, had somewhat higher amounts of coenzyme Q_{10} than fruit and vegetables [33]. However, normal dietary intake had little effect on coenzyme Q_{10} concentrations, and would be unlikely to affect bioequivalence estimates of the current study.

The importance of product formulation on coenzyme Q_{10} bioavailability has been suggested in earlier studies. In the present study product D, a marketed product containing non-solubilized coenzyme Q_{10} powder, was observed to be only minimally absorbed fol-

lowing a 180 mg dose (Fig. 2). Based upon these results it can be predicted that only slight increases in coenzyme Q_{10} plasma concentration will occur with chronic supplementation of a product containing this non-solubilized powder form of $Q_{10.}$ All clinicians need to be aware of this bioavailability problem, because many of the OTC products marketed in the USA and other countries contain this non-solubilized Q_{10} powder. Dietitians and nutritionists should educate health care providers and the general public about these product differences.

Because of the insolubility of coenzyme Q_{10} in water, a variety of formulations have been developed to solubilize the agent and promote absorption. An earlier study tested the bioequivalence of four oral coenzyme Q_{10} formulations in ten healthy volunteers, and reported a 35% increase in area under the concentration-time curve (AUC) following administration of coenzyme Q_{10} in soy bean oil vs. various emulsifying agents [20]. In another report following 4 weeks of continuous coenzyme Q_{10} dosing (120 mg/day), Chopra et al found a 2.5- to three-fold increase in bioavailability for a formulation containing fully-solubilized coenzyme Q_{10} (Q-Gel™) compared to other commercial products [22]. The Q-Gel™ formulation used in their study is identical to product C (UbiQGel®) selected as the reference product for the current study.

The current study shows that the new formulation (product B or Q-Nol™) of coenzyme $Q_{10,}$ which contains the reduced form (ubiquinol), has increased bioavailability compared to the fully-solubilized reference formulation. The liquid preparation (product A or LiQ-10™), has increased bioequivalence compared to the reference product C, but did not reach a statistically significant difference. The liquid formulation may by useful for individuals who have difficulty or are unable to swallow solid formulations. Further studies are needed to determine whether these new products will provide significantly higher coenzyme Q_{10} concentrations with chronic dosing. All four products tested were well tolerated in fasting adults. Because of inter-individual and inter-product variability in coenzyme Q_{10} absorption, it is advisable that coenzyme Q_{10} plasma concentrations be monitored in patients receiving supplementation to assure dosing adequacy and document compliance.

Acknowledgments

Dr. M. Miles was the principal investigator of this study, recruiting subjects, and pharmacokinetic data analysis. Dr. P. Horn analyzed data. Dr. L. Miles processed samples and helped write the final manuscript. Dr. P. Tang performed the plasma coenzyme Q_{10} analysis. Dr. P. Steele provided laboratory screening and lipid profile testing. Dr. T. DeGrauw provided medical screening and supervision. The products tested in this study were provided by the Tishcon Corporation, Westbury, NY, USA. This study supported in part by a grant from the Tishcon Corporation, Westbury, NY, USA. Dr. M. Miles has served as a consultant for the Tishcon Corporation in the past. None of the authors has any financial or employment relationship with the Tishcon Corporation.

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