

# Summary Report

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## Coenzyme Q10

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Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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## REVIEW OF NOMINATIONS

Coenzyme Q10 (CoQ10; UNII code: EJ27X76M46) was nominated for inclusion on the 503B Bulks List by Empower Pharmacy and Sincerus Florida, LLC. While the exact medical condition for which the compounded drug is being requested is generally unknown, CoQ10 is generally used to treat inherited primary CoQ10 deficiency resulting in mitochondrial disorders and CoQ10 deficiency associated cardiovascular disease. Additionally, CoQ10 will be used in free radical reduction and to increase the antioxidant capacity of the skin. CoQ10 will be compounded as oral capsules and solutions and an intramuscular solution for injection in strengths ranging from 25-100mg/mL, 25-200mg, and 10-20mg/mL. Additionally, CoQ10 will be compounded as a topical 1.5% product as requested by the prescriber. The reason provided for nomination to the 503B Bulks List is there are no FDA-approved products that contain CoQ10.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of CoQ10 products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA) and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA) and approval status provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for CoQ10; name variations of CoQ10 were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing CoQ10. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

### *Systematic literature review*

#### Search strategy

Two databases (PubMed and Embase) were searched including any date through February 22, 2019. The search included a combination of ("Coenzyme Q10"[TIAB] OR Ubidecarenone[TIAB] OR "Ubiquinone 50"[TIAB] OR CoQ10[TIAB] OR "Ubiquinone 50"[TIAB] OR Ubisemiquinone[TIAB] OR "Q-ter"[TIAB]) AND (treat\*[TIAB] OR therap\*[TIAB] OR clinic\*[TIAB] OR deficiency[TIAB] OR mitochondria\*[TIAB] OR antioxidant[TIAB] OR "free radical"[TIAB] OR cardiovascular[TIAB])

OR heart[TIAB] OR vascular[TIAB] OR skin[TIAB] OR hypertension[TIAB] OR derm\*[TIAB] OR cardio\*[TIAB]) AND (humans[MeSH Terms] AND English[lang] NOT autism). Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

### Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of CoQ10 or the implementation of CoQ10 in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

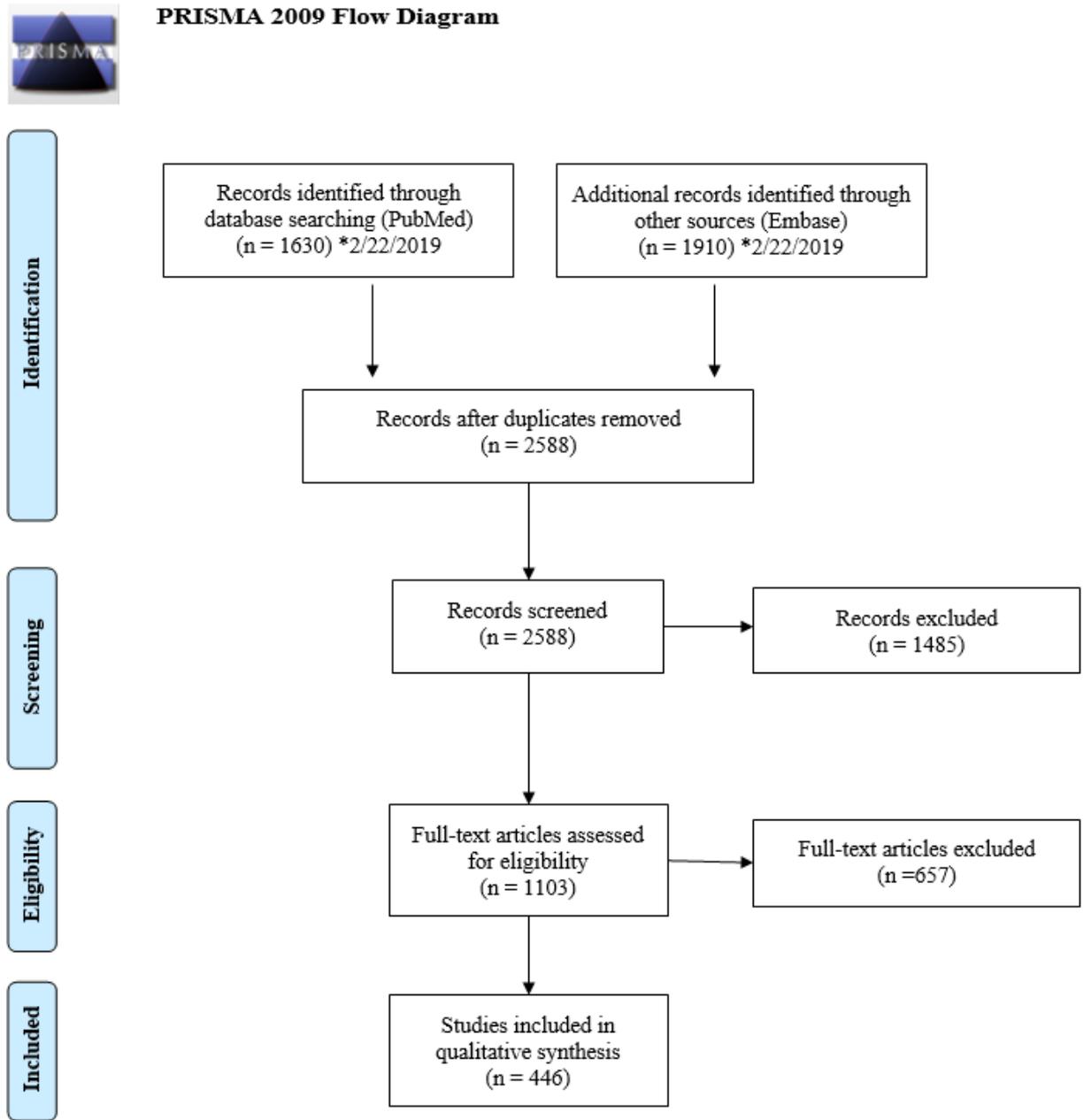
### Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for CoQ10 use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of CoQ10 compared to alternative therapies.

### Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

### *Outreach to medical specialists and specialty organizations*

Using the indications from the nominations and the results of the literature review, 12 medical specialties that would potentially use CoQ10 were identified: cardiology, dentistry, dermatology, endocrinology, naturopathy, neurology, oncology, oral medicine, primary care, psychiatry, pulmonology, and urology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Six (6) medical experts were contacted for interviews of which two (2) accepted. Medical experts in dentistry, neurology, oncology, and psychiatry were contacted for an interview however all four (4) medical experts failed to respond to the interview request. The interviews were recorded and transcribed via ©Rev.com. QSR International's Nvivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

### *Survey*

General professional medical associations and specialty associations for cardiology, dentistry, dermatology, endocrinology, naturopathy, neurology, oncology, oral medicine, primary care, psychiatry, pulmonology, and urology, identified from the nominations, literature review, and interview, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 16 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

<b>Specialty</b>	<b>Association</b>
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Naturopathy	American Association of Naturopathic Physicians (AANP)
Oral Medicine	American Academy of Oral Medicine (AAOM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

<b>Specialty</b>	<b>Association</b>	<b>Reasons for Declining</b>
Dentistry	American Dental Association (ADA)	Declined - ADA concluded that this issue does not affect enough dentists to warrant a significant investment of time”
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, “Endocrinologists are not generally in the compounding space.”
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Oncology	American Society of Clinical Oncology (ASCO)	Declined
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Psychiatry	American Psychiatric Association (APA)	Declined, “we have put this ask to our members and unfortunately, we have not received any information on psychiatrists using compounded products”
Pulmonology	American Thoracic Society (ATS)	Declined
Urology	American Urology Association (AUA)	Declined, “our physicians are inundated with surveys and I’m afraid you won’t be able to get the information you need”

## CURRENT AND HISTORIC USE

### *Summary of background information*

- CoQ10 is not available as an FDA-approved product.
- CoQ10 is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for CoQ10.
- CoQ10 is available in Abu Dhabi. CoQ10 is available in Australia and Hong Kong as a single-agent OTC product and in Latvia as a combination product.

Table 3. Currently approved products – US

*No approved products in the US*

Table 4. Currently approved products – select non-US countries and regions<sup>a</sup>

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date
Coenzyme Q10	30-100mg	Capsule	–	Abu Dhabi	Active	–

Abbreviations: “–”, not mentioned; ROA, route of administration.

<sup>a</sup>Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, route of administration and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations. See Methodology for full explanation.

### Summary of literature review

- Total number of studies included: 446 studies (189 descriptive, 229 experimental, and 28 observational).
- Most of the studies were from the US (101).
- The most common indication for the use of CoQ10 in the US were CoQ10 deficiency and statin-induced adverse effects. The most common indications from the non-US studies were CoQ10 deficiency, statin-induced adverse effects, cardiomyopathy, diabetes, heart failure, hyperlipidemia, migraine, and mitochondrial disorder.
- Compounded products were identified from both US and non-US studies, in the nominated formulations.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive <sup>1-189</sup>	189
Experimental <sup>190-418</sup>	229
Observational <sup>419-446</sup>	28

Table 6. Number of studies by country

Country	Number of Studies
Argentina <sup>226</sup>	1
Armenia <sup>176</sup>	1
Australia <sup>74,127,141,151,160,178,214,239,264,345</sup>	10
Austria <sup>26,80,180</sup>	3
Brazil <sup>10,23,129,140,350,392,444</sup>	7
Canada <sup>33,58,62,63,108,154,242,263,312,374,439</sup>	11
China <sup>32,36,47,89,110,112,113,117-119,177,182-184,188,235,236,283,411,412</sup>	20
Columbia <sup>381</sup>	1
Croatia <sup>265</sup>	1
Czech Republic <sup>189</sup>	1
Denmark <sup>72,128,130,351,352</sup>	5
Ecuador <sup>171</sup>	1

Egypt <sup>193,422</sup>	2
France <sup>14,35,302,368,393</sup>	5
Georgia <sup>232</sup>	1
Germany <sup>5,78,91,97,231,247,294,330,363,402</sup>	10
Greece <sup>400</sup>	1
Hong Kong <sup>252</sup>	1
Hungary <sup>82,281</sup>	2
India <sup>66,121,158,163-165,172,194,303,323,333,353,384,394-396,435</sup>	17
Indonesia <sup>123</sup>	1
Iran <sup>53,70,79,84,95,96,125,133,147,185,196,203,250,251,267,271,274-277,279,295,317,344,346,367,377,378,382,386,388,416,445</sup>	33
Iraq <sup>197,199</sup>	2
Ireland <sup>27,144,332</sup>	3
Israel <sup>17,25,57,152,219,246,326</sup>	7
Italy <sup>24,28-30,54,56,99,120,122,124,126,142,149,157,167,174,207-213,215-218,220,225,227,233,234,240,241,249,253,254,258-262,273,280,282,284,285,291,301,307,331,335-342,348,349,366,371,373,380,383,424,425,426,442</sup>	70
Japan <sup>2,59,81,83,88,92,93,132,135,159,170,173,206,290,298,304,313,321,356,357,389,390,403-406,430,433,434,443,446</sup>	31
Latvia <sup>324</sup>	1
Mexico <sup>15,369</sup>	2
New Zealand <sup>187</sup>	1
Nigeria <sup>136</sup>	1
Norway <sup>221</sup>	1
Pakistan <sup>198</sup>	1
Poland <sup>41,248,401</sup>	3
Portugal <sup>153,286</sup>	2
Romania <sup>407</sup>	1
Russia <sup>137,266</sup>	2
Saudi Arabia <sup>270</sup>	1

Serbia <sup>85</sup>	1
Singapore <sup>111,387</sup>	2
Slovakia <sup>60,69,362</sup>	3
Slovenia <sup>397,438</sup>	2
South Korea <sup>195,315</sup>	2
Spain <sup>11-13,38,39,228,230,244,245,300,358,359,365</sup>	13
Sweden <sup>77,150,223,347</sup>	4
Switzerland <sup>3,76,268,409</sup>	4
Taiwan <sup>34,37,179,237,238,437</sup>	6
Thailand <sup>318,399</sup>	2
Turkey <sup>6,16,43,44,49,51,64,68,87,94,168,204,205,272,292,414,415,431,432</sup>	19
Ukraine <sup>314,364</sup>	2
UK <sup>21,146,169,243,306,328</sup>	6
US <sup>1,7-9,18,20,22,31,40,45,52,61,65,71,73,75,86,90,98,100-107,109,114-116,131,134,138,139,143,145,148,156,161,162,166,181,190-192,200,201,222,224,229,255,256,269,278,287-289,293,296,297,305,309,310,319,320,325,327,329,334,343,354,355,361,370,372,376,379,391,398,417-421,427-429,436,440,441</sup>	91
Multiple Countries <ul style="list-style-type: none"> <li>• Italy, US<sup>42,408</sup></li> <li>• Italy, Brazil, US<sup>48</sup></li> <li>• Italy, France, US, Spain<sup>155</sup></li> <li>• Belgium, The Netherlands, US, Sweden<sup>175</sup></li> <li>• South Korea, US, Japan<sup>186</sup></li> <li>• Qatar, Egypt, US<sup>202</sup></li> <li>• US, China<sup>311</sup></li> <li>• US, France, UK<sup>316</sup></li> <li>• Japan, US<sup>413</sup></li> <li>• Austria, Switzerland<sup>322</sup></li> <li>• Belgium, Luxembourg, Spain<sup>257,385</sup></li> <li>• Chile, Spain<sup>55</sup></li> <li>• Denmark, Finland<sup>50</sup></li> <li>• Greece, Italy<sup>360</sup></li> <li>• Italy, Spain<sup>308</sup></li> <li>• Italy, UK<sup>46</sup></li> <li>• Switzerland, Belgium<sup>375</sup></li> <li>• Turkey, Austria<sup>423</sup></li> <li>• Turkey, Switzerland<sup>4</sup></li> <li>• UK, Germany<sup>410</sup></li> </ul>	22

TotalUS <sup>a</sup> : 101
TotalNon-US Countries <sup>a</sup> : 352

<sup>a</sup>Studies 42,48,155,175,186,202,311,316,408,413 counted in both US and non-US total.

Table 7. Number of studies by combinations

*No combination product(s) were nominated*

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
CoQ10 deficiency <sup>20,48,52,131,145,278,297,354,355,427</sup>	100-3000mg/day 7.9-12mg/kg/day	–	–	Oral	5 months-4 years
Statin-induced adverse effects (dyspnea, fatigue, memory loss, peripheral neuropathy <sup>104</sup> , ALS <sup>65</sup> , LV dysfunction <sup>161</sup> , myalgia <sup>31,104,116,138,222,229</sup> )	100-600mg/day	–	Capsule	Oral	30 days-3 months
Amyotrophic lateral sclerosis <sup>109</sup>	1800-2700mg/day	–	–	–	9 months
Congestive heart failure <sup>71,162,309,376,436</sup>	90-300mg/day	–	Capsule	Oral	16 weeks-19 months
Hypertension <sup>100,101,224,287,413</sup>	30-600mg/day	–	Capsule, tablet	Oral	8 days-5 months
Cardiomyopathy <sup>100,102,103,106</sup>	75-600mg/day	–	Capsule, tablet	Oral	–
Diastolic dysfunction <sup>100,105</sup>	75-600mg/day	–	Capsule, tablet	Oral	–
Improve survival post cardiac arrest <sup>255</sup>	250-450mg/day	–	Liquid	Oral	5 days
Valvular heart disease (VHD) and mitral valve prolapse (MVP) <sup>100</sup>	75-600mg/day	–	Capsule, tablet	Oral	–
Myocardial disease <sup>107</sup>	99mg/day	–	–	Oral	12 weeks
Myocardial preservation during heart surgery <sup>86</sup>	100mg/day	–	–	Oral	44 days
Orthostatic hypotension <sup>370</sup>	220-294mg/day	–	–	Oral	7-13 months
Parkinson's disease <sup>191,192,269,319,391</sup>	1300-2400mg/day	–	Wafers	Oral	12-16 months
Progressive supranuclear palsy (PSP) <sup>200,201</sup>	1200-2400mg/day	–	–	–	12 months
Huntington disease <sup>190,343</sup>	600-2400mg/day	–	Tablet, wafers	Oral	30-60 months
Spinocerebellar ataxia <sup>20,98,329</sup>	100-2400mg/day	–	–	–	1-139 months

Ataxia with oculomotor apraxia type 2 (AOA2) <sup>256</sup>	1200mg	–	–	–	–
Mitochondrial myopathy <sup>1,22,361,419</sup>	150-900mg/day	–	–	Oral	10 months
Mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) <sup>8,143,325,327</sup>	–	–	–	–	–
Metabolic syndrome <sup>408</sup>	30mg/day	–	Tablet	–	2 months
Mitochondrial sensorineural hearing loss (SNHL) <sup>9</sup>	150mg/day	–	–	–	1 year
Mitochondrial DNA depletion syndrome <sup>61,316</sup>	300-2000mg/day	–	–	–	5 years
Progressive muscular dystrophies and neurogenic atrophies <sup>428</sup>	99mg/day	–	Capsule	Oral	3 months
Limb-girdle syndrome <sup>428</sup> due to POLG1 mutation <sup>311</sup>	99mg/day	–	Capsule	Oral	3 months
Duchenne muscular dystrophy <sup>166,428</sup>	90-800mg/day	–	Capsule, tablet	Oral	3-6 months
Corneal Edema in Kearns-Sayre <sup>320</sup>	50-100mg/day	–	–	–	–
Breast cancer <sup>114,115,441</sup>	90-390mg/day	–	–	Oral	–
Treatment-induced fatigue in breast cancer <sup>156,440</sup>	300mg/day	–	Capsule	Oral	24 weeks
Fatigue <sup>421</sup>	–	–	–	–	–
Advanced metastatic adenocarcinoma <sup>134</sup>	110mg/kg	–	Lipid nanodispersion	Intra venous	144 hours
Peritoneal cancer <sup>429</sup>	150mg/day	–	Capsule	Oral	–
Prevention of adriamycin (ADM) cardiotoxicity <sup>40</sup>	50mg/day	–	Tablet	Oral	5 months
Migraine <sup>73</sup> prophylaxis <sup>372,398</sup>	1-3mg/kg/day	–	Capsule	Oral	–
	100-150mg/day		Chewable tablet	–	90-112 days
Bipolar depression <sup>417</sup> in geriatrics <sup>288</sup>	400-1200mg/day	–	–	Oral	31 days-8 weeks

Drug-induced leukoencephalopathy (DIL) <sup>7</sup>	–	–	–	–	–
Ethylmalonic encephalopathy <sup>186</sup>	50mg/kg	–	–	–	–
Infantile encephalomyopathy and nephropathy <sup>155</sup>	30mg/kg/day	–	–	Oral	–
U-47700 provoked Delayed posthypoxic leukoencephalopathy <sup>18</sup>	–	–	–	–	–
Antia ging for skin <sup>296</sup>	–	–	Cream	Topical	12 weeks
Hyperpigmentation and photodamaged skin <sup>305</sup>	–	–	Moisturizer	Topical	12 weeks
Antioxidant for male infertility <sup>202</sup>	–	–	Tablet	Oral	3 months
Cystic fibrosis <sup>379</sup>	–	–	Capsule	Oral	16 weeks
Chronic obstructive pulmonary disease <sup>42</sup>	320mg/day	–	–	Oral	8 weeks
Cocaine dependence <sup>148</sup>	200mg/day	–	Capsule	–	8 weeks
Leigh’s syndrome <sup>175</sup>	300mg/day	–	–	–	At least 6 weeks
Myelodysplastic syndrome <sup>293</sup>	1200mg/day	–	Wafers	Oral	At most 12 months
Paroxysmal leg pain <sup>418</sup>	–	–	–	–	–
Periodontal disease <sup>181</sup>	50mg/day	–	Capsule	Oral	3 weeks
Syncope <sup>139</sup>	–	–	–	–	–

Abbreviations: “–”, not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Aciduria <sup>49,85,174,246</sup>	2.4-5mg/kg/day 100-200mg/day	–	Wafer	Oral	3-6 months
Acute myocardial infarction <sup>97,396</sup>	100-120mg/day	–	Capsule	Oral	4 weeks-1 year
Cancer <sup>108,373</sup>	400mg/day	–	Tablet	–	3 years
HIV/AIDS <sup>214,220</sup>	2-200mg/day	–	–	Oral	12 weeks-3 months
Anthra cyclines cardiotoxicity <sup>307</sup>	200mg/day	–	–	–	–
Anti-NMDAR encephalitis	800mg/day	–	–	Nasogastric	–
Antioxidant vitamin deficiency <sup>395</sup>	60-180mg/day	–	Capsule	Oral	21 days-4 weeks
Asthma <sup>69</sup>	120mg/day	–	–	–	16 weeks
Bipolar depression <sup>185,344</sup>	200mg/day	–	Tablet	Oral	8 weeks
Bell's palsy <sup>198</sup>	100mg/day	–	–	Oral	1 month
Cardiomyopathy <sup>21,92,95,119,142,173,194,254,336,363,384,399</sup>	2-10mg/kg/day 30-210mg/day	–	Capsule	Oral	21 days-14.5 months
Chemoprotective effect on lipid in paint and lacquer industry workers <sup>248</sup>	30mg/day	–	Capsule	Oral	4 weeks
Chronic fatigue syndrome <sup>83,141,345,392</sup>	100mg/day	–	Capsule	Oral	30 days
	30mg/day		Jelly		21 days
	200mg/day		–		16 weeks

Periodontitis <sup>304</sup>	0.9g/day	–	Capsule	Oral	6 weeks
Ischemic/coronary heart disease <sup>364</sup>	–	85mg/mL	Solution	Topical	–
Cerebellar ataxias <sup>286</sup>	–	–	–	–	–
Chronic lung disease <sup>59</sup>	90mg/day	–	–	–	8 weeks
Chronic progressive external ophthalmoplegia <sup>118,264</sup>	200-300mg/day	–	–	Oral	3 years
Chronic renal disease <sup>127,164, 394,430</sup>	180-200mg/day	–	Capsule	Oral	4-12 weeks
	30mg/day	–	Solution		12 weeks
Chronic tinnitus aurium <sup>91</sup>	300mg/day	–	–	–	12 weeks
Clomiphene-citrate-resistant polycystic ovary syndrome <sup>158,422</sup>	180mg/day	–	Capsule	Oral	–
Cobalamin C defect-hemolytic uremic syndrome <sup>4</sup>	5mg/kg/day	–	–	Oral	Indefinite
Corneal epithelial wound healing promotion <sup>68,432</sup>	200-400mg/day	–	Drop	Ophthalmic	2 weeks-2 months
Community-acquired pneumonia in elderly <sup>276</sup>	200mg/day	–	Capsule	Oral	14 days
Chronic obstructive pulmonary disease <sup>42,339</sup>	160-320mg/day	–	Capsule	Oral	8 weeks-2 months
Diabetes <sup>50,72,79,96,196,199,223,239,262,266,267,274,275,290,295,347,386,393,404</sup>	100-1000mg/day	–	Capsule	Oral	8 weeks-6 months
	20-60mg/day 1mg/kg/day		Tablet		4-6 months
	100-200mg/day		–		3-6 months
Dry eye <sup>366</sup>	–	–	Drop	Ophthalmic	12 weeks
Dry mouth <sup>443</sup>	100mg/day	–	Capsule	Oral	1 month
Ethylmalonic encephalopathy <sup>87,186</sup>	10-50mg/kg	–	–	–	–

Exercise <sup>64,88,230,271,292,306,348,383,431</sup>	200mg/day	–	Tablet	Oral	8 weeks
	100-200mg/day	–	Capsule		8-12 weeks
	50-300mg/day	–	–		14 days-4 weeks
Extracorporeal shockwave lithotripsy (ESWL) <sup>228</sup>	200mg/day	–	–	Oral	2 weeks
Friedreich's ataxia (FRDA) <sup>243</sup>	100-300mg/day 9mg/kg/day	–	Capsule	Oral	6 months - 2 years
Fibromyalgia <sup>11,38,39,193,244,328,358,359</sup>	200-300mg/day	–	Capsule	Oral	40 days - 3 months
			–		12-24 weeks
	2mg/kg/day		–	6 months	
Gingival inflammation reduction <sup>121</sup>	120mg/day	–	–	Oral	3 months
Glaucoma <sup>308</sup>	–	–	–	Topical	4 weeks
Glutaric acidemia type II <sup>15,16,416</sup>	–	–	–	–	–
Headache <sup>245,270,381,424,425,442</sup>	300mg/day	–	Capsule	Oral	3 months
	200mg/day		Tablet		2 months
	200mg/day		–		3-12 months
Hearing loss <sup>67,167,195,281,282,285,301,380</sup>	40-200mg/day	–	Capsule	Oral	7 days - 12 months
	160mg/day		Sachet		30 days
	600mg/day		Tablet		10 days
	30-160mg/day		–		30 days - 24 months
Hereditary spastic paraplegia (HSP) <sup>144</sup>	–	–	–	–	–

Heart failure <sup>77,81,99,128,130,137,149,188,206-208,215,216-219,291,312,342,349,351,352,367,410</sup>	200mg/day	-	Pearl	-	4 months
	150mg/day		Capsule		9 months
	60-200mg/day		Oral	3 months	
	30-320mg/day			7 days - 2 years	
	150mg/day			10.5-39.9 days	
	30-320mg/day 2mg/kg/day			7 days - 12 months	
	150-300mg/day		-	12 months - 2 years	
Hyperlipidemia <sup>60,120,122,,232,338,240,241,249,337,346,435</sup>	2-400mg/day	-	Capsule	Oral	4-12 weeks
	6mg/day		Solution		16 weeks
	2-50mg/day		Tablet		6 weeks - 12 months
	2-150mg/day		-		8 weeks - 6 months
Hypertension <sup>165,261,331,341,413</sup>	120mg/day	-	Capsule	Oral	8 weeks
	2mg/day		Tablet		6 months
	15-100mg/day		-		8 days - 5 months
Infantile encephalomyopathy and nephropathy <sup>155</sup>	30mg/kg/day	-	-	Oral	-
Increase antibody tier in hepatitis B vaccination <sup>210</sup>	30-180 mg	-	Capsule	Oral	14 days
Influenza B-induced rhabdomyolysis <sup>154</sup>	-	-	-	-	-
Leber's hereditary optic neuropathy <sup>34,35,47,437</sup>	90-250mg/day	-	-	Oral	4 months - 2 year

Infertility <sup>202,326,377</sup> (Asthenozoospermia <sup>66,93,197,209,300</sup> , Asthenoteratozoospermia <sup>26,225</sup> , In vitro fertilization <sup>160,226,374</sup> , Obstructive azoospermia <sup>303</sup> , Poor ovarian reserve <sup>62</sup> , Poor ovarian response <sup>183</sup> , Sub- fertility <sup>80</sup> , Varicocele <sup>56,284</sup> )	30mg/day	-	Caplet	Oral	3 months
	200mg/day		Softgel		6 months
	100-200mg/day		Tablet		3-6 months
	15-1200mg/day		-		60 days - 12 months
	150-600mg/day		-	-	6 months
Kearns-Sayre Syndrome <sup>24,58,89,180,264,356</sup> Hypoparathyroidism <sup>360</sup>	60-300mg/day	-	-	Oral	11 months - 3 years
Leigh Syndrome <sup>36,43,44,117,175,179</sup>	50mg/kg/day 90-300mg/day	-	-	Oral	6 weeks - 1 year
Limb-girdle muscular dystrophy type 2B <sup>311,412</sup>	-	-	-	-	-
Lipid storage myopathy <sup>177</sup>	30-120mg/day	-	-	-	At least 9 months
Maternally inherited diabetes and deafness (MIDD) <sup>22,74,263,403,444</sup>	100-300mg/day	-	-	Oral	1 year - 3 years
Metabolic Syndrome <sup>187,335,340,390,408</sup>	-	-	-	Intra venous	-
	15-30mg/day		Tablet	Oral	2-12 months
	30mg/day		-	-	2 months
Methylmalonic acidemia (MMA) <sup>76,365,409</sup>	180-200mg/day	-	-	-	-
Migraine <sup>51,70,133, 253,260,317</sup> prophylaxis <sup>227,250,251,294,302,375,438,445</sup>	30-100mg/day	-	Tablet	Oral	8 weeks - 3 months
	100-400mg/day		Capsule		3 months
	300mg/day		Solution		3 months
	50mg/day		-	-	-

Mitochondrial cytopathy <sup>211,212,323</sup>	150mg/day	–	–	–	6 months
Mitochondrial disorder <sup>10,63,123,140,182,252,316,321,433</sup>	55mg/kg/day 30-100mg/day	–	Capsule	Oral	14 days - 3 years and 8 months
Mitochondrial encephalomyopathy <sup>3,135, 237,314,371,389,406</sup>	120-160mg/day 4-5mg/kg/day	–	–	Oral	5 days - 6 months
Mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) <sup>2,17,37,74,159,298,313,434,446</sup>	30-300mg/day	–	–	Oral	At least 1 month
Mitochondrial myopathy <sup>28-30,150,157,231,322,368</sup>	2-5mg/kg/day 120-200mg/day	–	–	Oral	6 months - 1 year
Myopathy, lactic acidosis, and sideroblastic anemia (MLASA) <sup>168</sup>	–	–	–	–	–
Multiple acyl-coenzyme A dehydrogenase deficiency (MADD) <sup>6,112,279,299</sup>	200-300mg	–	–	Oral	–
Multiple sclerosis <sup>124,382,388</sup>	200-500mg/day	–	Capsule	Oral	3 months
Myelodysplastic syndrome <sup>57</sup>	180mg/day	–	–	Oral	6-12 months
Myoclonic epilepsy with ragged red fibers (MERRF) <sup>265</sup>	–	–	–	–	–
Nephrotic syndrome <sup>176,204,205,401</sup>	20-30mg/kg/day 300mg/day	–	–	Oral	3-22 months
Non-alcoholic fatty liver disease <sup>53,84,125,277</sup>	100mg/day	–	Capsule	Oral	4 weeks - 3 months
Oxidative stress in renal transplant <sup>41</sup>	90mg/day	–	–	Oral	4 weeks
Parkinson's disease <sup>110,330,387</sup>	300-2400mg/day	–	–	–	4 weeks - 18 months
Peyronie's disease <sup>378</sup>	300mg/day	–	Tablet	Oral	24 weeks
Periodic paralysis <sup>248</sup>	30mg/day	–	Capsule	Oral	4 weeks

Post-cataract surgery <sup>426</sup>	–	0.1%	Solution	Topical	9 months
Praeder–Labhart–Willi Syndrome <sup>268</sup>	20mg/kg/day	–	Solution	Oral	1 year
Prevention adverse effect of isotretinoin <sup>273</sup>	–	–	–	Oral	6 months
Prevention of contrast-induced nephropathy in patients with CHD and renal dysfunction <sup>235,236</sup>	60mg/day	–	–	Oral	5 days
Prevention of myocardial injury during cardiac operation <sup>169,203,233,333</sup>	50–300mg/day	–	Capsule	Oral	1–10 days
Prevention of pre-eclampsia in pregnancy <sup>171</sup>	200mg/day	–	Capsules	Oral	–
Primary coenzyme Q10 deficiency <sup>5,12–14,19,21,25,27,32,33,48,78,82,94,117,126,146,184,257–259,272,283,385,400,407,415,423,439</sup>	1.5-50 mg/kg/day 60-2500 mg/day	–	Softgel	Oral	2 months
Promote skin condition <sup>46</sup>	20mg/day	–	Pearl	Oral	4 weeks
Progressive supra nuclear palsy <sup>402</sup>	5mg/kg	–	Emulsion	Oral	6 weeks
Progressive symmetrical facial lipoatrophy due to discoid lupus erythematosus <sup>414</sup>	90mg/day	–	Tablet	Oral	3 months
Prophylaxis of postoperative low cardiac output <sup>179</sup>	30-60mg/day	–	–	Oral	6 days
Protection from tissue reperfusion injury during abdominal aortic cross-clamping <sup>234</sup>	50-150mg/day	–	–	Oral	7 days
Respiratory chain disorder <sup>153,315</sup>	5mg/kg/day	–	–	Oral	46 months
Schizophrenia <sup>332</sup>	300mg/day	–	Capsules	Oral	6 months
Sickle cell disease <sup>172</sup>	–	–	–	–	6 months
Stable angina <sup>342</sup>	60mg/day	–	–	Oral	4 weeks
Statin-induced adverse effects <sup>362</sup> (rhabdomyolysis <sup>54,113,152,178,189,213,221,280,324,397</sup> , hepatopathy <sup>111,411</sup> , memory dysfunction <sup>136</sup> , cerebellar ataxia <sup>129,350</sup> )	60–400mg/day	–	Capsule	Oral	5 days – 6 months

Stroke <sup>55,147,353</sup>	100-300mg/day	–	Capsule	Oral	4 weeks – 1 year
Subacute visual impairment in HMSN VI (hereditary motor sensory neuropathy type VI) <sup>405</sup>	200mg/day	–	–	Oral	8 months
Tuberous sclerosis <sup>163</sup>	90mg/day	–	–	–	12 weeks
Warfarin induced hair loss <sup>132</sup>	30mg/day	–	–	–	–
X-linked adrenoleukodystrophy <sup>242</sup>	50-60mg/day	–	–	Oral	12 years
Zidovudine (ZDV)–induced myopathy <sup>151</sup>	0.7-4mg/kg 50-300mg/day	–	–	–	4 years

Abbreviations: “–”, not mentioned; ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Cardiomyopathy <sup>102,103</sup>	1988-1990	<ul style="list-style-type: none"> <li>33.3mg in soybean oil, which was encased in a sealed, soft gelatin capsule</li> </ul>	Capsule	–
Fibromyalgia (mitochondrial myopathy) <sup>1</sup>	2012	<ul style="list-style-type: none"> <li>–</li> </ul>	–	–

Abbreviation: “–”, not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Periodontitis <sup>304</sup>	<ul style="list-style-type: none"> <li>Dispersed into soybean oil</li> </ul>	Solution	85mg/ml

*Summary of focus groups/interviews of medical experts and specialty organizations*

Two (2) interviews were conducted.

Table 12. Overview of interviewee

<b>Interviewee</b>	<b>Level of Training</b>	<b>Specialty</b>	<b>Current Practice Setting</b>	<b>Experience with CoQ10</b>	<b>Interview Summary Response</b>
DER_06	MD	Dermatology/ Immunology	Consulting	Not specified	<ul style="list-style-type: none"> <li>There is no need for CoQ10 in the office (can prescribe if needed).</li> </ul>
END_03	MD	Endocrinology		Yes	<ul style="list-style-type: none"> <li>Uses as the OTC formulation, not compounded</li> <li>Most commonly used when patients have muscle issues with statins</li> <li>No good data but some people find a benefit and is probably not harmful</li> </ul>

Abbreviation: MD, Doctor of Medicine.

*Summary of survey results*

Table 13. Characteristics of survey respondents [23 people responded to the survey<sup>a</sup>]

<b>Board Certification</b>	<b>DMD/DDS</b>	<b>MD</b>	<b>ND</b>	<b>No response</b>
Fellow of the American Board of Naturopathic Oncology	0	0	1	0
Naturopathic Doctor	0	0	6	0
Naturopathic Physician	0	0	5	0
Oral medicine	2	0	0	0
Pain medicine	1	0	0	0
Sleep medicine	1	0	0	0
No Board certification	0	1	3	0
No response	0	0	0	11

Abbreviations: DMD/DDS, Doctor of Medicine in Dentistry; MD, Doctor of Medicine; ND, Naturopathic Doctor.

<sup>a</sup>Some respondents reported more than one terminal clinical degree or board certification.

Table 14. Types of products used, prescribed, or recommended

<b>Types of Products</b>	<b>Respondents, n (N=15<sup>a</sup>)</b>
Compounded	0
FDA-approved	0
Over-the-counter	4
Dietary	11
Unsure	0
No response	3

<sup>a</sup>Out of 23 respondents, 15 reported using, prescribing, or recommending multiple types of CoQ10 product.

Table 15. Compounded use of CoQ10 in practice

*No survey respondents provided this information*

Table 16. Indications for which CoQ10 is considered a standard therapy

<b>Indication</b>	<b>Standard Therapy</b>		
	<b>Compounded, n (N=0)</b>	<b>Non-compounded, n (N=12<sup>a</sup>)</b>	<b>No response, n (N=3)</b>
Cardiovascular disease	0	4	0
Congestive heart failure	0	4	0
Diabetes	0	2	0
Dry mouth	0	1	0
Fatigue	0	2	0
General antioxidant	0	1	0
Hypertension	0	1	0
Kidney failure/disease	0	2	0
Mitochondrial disease	0	2	0
Myalgia	0	2	0
Parkinson's disease	0	1	0
Statin treatment	0	4	0

Tinnitus	0	1	0
Other <sup>b</sup>	0	1	0
No response	0	0	3

<sup>a</sup>Some respondents reported more than one indication.

<sup>b</sup>“Varies depending on individual patient circumstances”.

Table 17. Reasons for using compounded product instead of the FDA–approved products

*No survey respondents provided this information*

Table 18. Change in frequency of compounded CoQ10 usage over the past 5 years

*No survey respondents provided this information*

Table 19. Do you stock non–patient specific compounded CoQ10 in your practice?

*No survey respondents provided this information*

Table 20. Questions related to stocking non–patient specific compounded CoQ10

*No survey respondents provided this information*

## CONCLUSION

Coenzyme Q10 (CoQ10; UNII code: EJ27X76M46) was nominated for inclusion on the 503B Bulks List by Empower Pharmacy and Sincerus Florida, LLC. While the exact medical condition for which the compounded drug is being requested is generally unknown, CoQ10 is generally used to treat inherited primary CoQ10 deficiency resulting in mitochondrial disorders and CoQ10 deficiency associated cardiovascular disease. Additionally, CoQ10 will be used in free radical reduction and to increase the antioxidant capacity of the skin. CoQ10 will be compounded as oral capsules and solutions and an intramuscular solution for injection in strengths ranging from 25-100mg/mL, 25-200mg, and 10-20mg/mL. Additionally, CoQ10 will be compounded as a topical 1.5% product as requested by the prescriber. Coenzyme Q10 is approved in Abu Dhabi, and available OTC in Australia, Hong Kong, and US.

From the literature review, the most common indications for the use of CoQ10 in the US were CoQ10 deficiency and statin–induced adverse effects. The most common indications from the non–US studies were CoQ10 deficiency, statin–induced adverse effects, cardiomyopathy, diabetes, heart failure, hyperlipidemia, migraine, and mitochondrial disorder. Compounded products were identified from both US and non–US studies, utilizing the nominated formulations.

From the interviews, compounded formulations were not identified as needed due to OTC availability.

From the survey responses, 15 out of 23 respondents used coenzyme Q10 but none utilized a compounded product.

## APPENDICES

### Appendix 1. References

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## Appendix 2. Survey instrument

### Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **coenzyme Q10**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871

Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: [compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu). If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or [hrpo@umaryland.edu](mailto:hrpo@umaryland.edu).

### End of Block: Welcome Page

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### Start of Block: Coenzyme Q10

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **coenzyme Q10**? Please check all that apply.

- Compounded drug product
- FDA-approved drug product
- Over the counter drug product
- Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- Unsure

*Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for coenzyme Q10? Please check all th... != Compounded drug product*

*Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for coenzyme Q10? Please check all th... = Compounded drug product*

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### Display This Question:

*If What type(s) of product(s) do you use, prescribe, or recommend for coenzyme Q10? Please check all th... = Compounded drug product*

Q2. Please list any conditions or diseases for which you use compounded **coenzyme Q10** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **coenzyme Q10** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- Single
- Combination

*Skip To: Q5 If Do you use compounded coenzyme Q10 as a single agent active ingredient, or as one active ingredient... != Combination*

*Display This Question:*

*If Loop current: Do you use compounded coenzyme Q10 as a single agent active ingredient, or as one active ingredient... = Combination*

Q4. Please list all combination products in which you use compounded **coenzyme Q10**.

\_\_\_\_\_

Q5. For which, if any, diseases or conditions do you consider compounded **coenzyme Q10** standard therapy?

\_\_\_\_\_

Q6. Does your specialty describe the use of compounded **coenzyme Q10** in medical practice guidelines or other resources?

\_\_\_\_\_

Q7. Over the past 5 years, has the frequency in which you have used compounded **coenzyme Q10** changed?

- Yes – I use it **MORE** often now (briefly describe why) \_\_\_\_\_
- Yes – I use it **LESS** often now (briefly describe why) \_\_\_\_\_

- No – use has remained consistent

Q8. Why do you use compounded [**substance**] instead of any FDA–approved drug product?

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Q9. Do you stock non–patient–specific compounded **coenzyme Q10** in your practice location?

- Yes
- No

*Skip To: End of Block If Do you stock non-patient-specific compounded coenzyme Q10 in your practice location? = No*

*Display This Question:*

*If Do you stock non-patient-specific compounded coenzyme Q10 in your practice location? = Yes*

Q10. In what practice location(s) do you stock non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

- Physician office
- Outpatient clinic
- Emergency room
- Operating room
- Inpatient ward
- Other (please describe) \_\_\_\_\_

Q11. How do you obtain your stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

- Purchase from a compounding pharmacy
- Purchase from an outsourcing facility
- Compound the product yourself
- Other (please describe) \_\_\_\_\_

Q12. Why do you keep a stock of non-patient-specific compounded **coenzyme Q10**? Please check all that apply.

- Convenience
- Emergencies
- Other (please describe) \_\_\_\_\_

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded coenzyme Q10? Please check all that apply. = Convenience*

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded coenzyme Q10? Please check all that apply. = Emergencies*

*Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded coenzyme Q10? Please check all that apply. = Other (please describe)*

Q13. For which, if any, diseases or conditions do you consider **coenzyme Q10** standard therapy?

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Q14. Does your specialty describe the use of **coenzyme Q10** in medical practice guidelines or other resources?

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**End of Block: Coenzyme Q10**

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**Start of Block: Background Information**

Q15. What is your terminal clinical degree? Please check all that apply.

- Doctor of Medicine (MD)
- Doctor of Osteopathic Medicine (DO)
- Doctor of Medicine in Dentistry (DMD/DDS)
- Naturopathic Doctor (ND)
- Nurse Practitioner (NP)
- Physician Assistant (PA)
- Other (please describe) \_\_\_\_\_

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- No Board certification
- Allergy and Immunology
- Anesthesiology
- Cardiovascular Disease
- Critical Care Medicine
- Dermatology
- Emergency Medicine
- Endocrinology, Diabetes and Metabolism
- Family Medicine
- Gastroenterology
- Hematology
- Infectious Disease
- Internal Medicine
- Medical Toxicology
- Naturopathic Doctor
- Naturopathic Physician
- Nephrology
- Neurology
- Obstetrics and Gynecology
- Oncology
- Ophthalmology
- Otolaryngology
- Pain Medicine
- Pediatrics
- Psychiatry
- Rheumatology
- Sleep Medicine
- Surgery (please describe) \_\_\_\_\_
- Urology
- Other (please describe) \_\_\_\_\_

**End of Block: Background Information**