AC-11® Claim Substantiation Document

Scientific data to support the Structure-Function health Claims of AC-11® patented, water soluble extract Of the bioactive components of the plant species Known as *Uncaria tomentosa*.

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AC-11® DSHEA Claim Support

1. Title of application

Scientific data to support the Structure-Function health claims of AC-11® patented, water soluble extract of the bioactive components of the plant species known as *Uncaria tomentosa*.

2. Sponsor and Preparer

Lee Anthony Worth
Regulatory and Technical Affairs
Optigenex, Inc.
333 River Street
Suite # 701
Hoboken, NJ 07030
Tel: 201-653-5607
Cell: 201-486-1741
tworth@optigenex.com

and

Daniel A. Zwiren
President and CEO
Optigenex Inc.
333 River Street
Hoboken, New Jersey 07030
Tel: 201-355-2098
Cell: 201-638-3810
dzwiren@optigenex.com

3. Application

Optigenex Inc. seeks claims registration for AC-11® (formerly known as C-MED-100®) a water soluble extract of the bio-active components of the plant species known as *Uncaria tomentosa*, a traditional medicinal plant indigenous to the Brazilian and Peruvian Rainforests. This registration application is presented to the [name of governmental health agency] responsible for regulating safe commercial distribution of nutrient supplements in [name of jurisdiction]. AC-11® is registered in the United States under DSHEA as a dietary supplement and also is registered by the Cosmetic Toiletry and Fragrance Association (CTFA) under the INCI name C1-8 Alkyl Tetrahydroxycyclohexanoate as a cosmetic ingredient. AC-11® is standardized to a minimum 8 % CAE ™, or Carboxy Alkyl Esters. CAE's ™ are the patented active ingredients in the composition. Moreover, recent research has confirmed that QAE ™, or Quinic Acid Analogs, a sub-classification of CAE™, are some of the biologically active Carboxy Alkyl Esters found in AC-11®. The Structure/Function claims for health benefits requested are:

1. Enhances natural DNA repair (ref. 6,8,11,12,13,15,17,18,19,21,22,23,26)*
2. Supports healthy immune system function (ref. 1,2,4,10,17,18,19,20,21,24,25)*
3. Increases repair of sun-damaged skin (ref. 5,6,7,8,11,25)*
4. Acts as a natural anti-inflammatory (ref. 1,2,5,23,24,25)*
5. Improves neurogenic lifestyle factor modulation (ref. 15,25,26)*
6. Improves anti-oxidant status (ref. 4,12,13,14,15,16,20,23)*
7. Increases collagen III expression in the skin (ref. 6)*

**See* references (pg.9-12)

A summary of the science presented in this application to support the aforementioned claims is presented in Table 1. There are twenty two (22) pertinent studies listed: four (4) are *in vitro*, six (6) are rodent studies, and twelve (12) are human studies. Four (4) of the studies were in the form of confidential reports to Optigenex. The clinical end points

evaluated were: increased DNA repair, enhanced immune response, antioxidation, anti-inflammation, collagen III production, and cell survival. The molecular mechanisms behind modulation of these clinical end points were documented by regulation of: (i) cancer cell toxicity; (ii) increased lymphocyte survival (increased half-life); (iii) enhanced DNA repair; (iv) Inhibition of NFkB; (v) reduced DNA damage; (vi) increases in WBC (white blood cells); (vii) increases in urinary tryptophan and nicotinamide levels; (viii) reduced risk from lifestyle factors (neurogenic); (ix) reduced 8-OH DNA adducts; (x) reduced UV induced sunburn cells; (xi) reduced levels of UV induced T-T dimers; (xii) enhanced collagen III synthesis; and (xiii) auditory nerve cell (OHC) repair. The data compiled involved the clinical assessments of greater than 200 animal and human specimens over a period in excess of twelve years. Although considered in most of the studies herein, there were no reports to suggest AC-11®, CAE or quinic acid analogs (QAE) cause any acute or chronic toxicity. AC-11®'s research and data provide strong evidence that the structure-function claims for health benefits are well founded in science.

Optigenex, Inc. seeks [name of country or jurisdiction] registration for two applications of AC-11®: (1) oral with a daily dose of 350mg/day, or in combination with other proven nutrients at 250mg/day; and (2) topical with 0.5 – 1.5% concentration in formula. Support for these doses and concentrations is documented in Table 1 by the reference papers cited therein. It should be noted, there was a major difference in doses for topical administration of AC-11® at 5 mg/ml or 0.5% concentration (total dose = 500mg/kg), compared to oral administration for skin, which was calculated as 250 mg/day x 4 days, which equaled a total dose of 14.3 mg/kg AC-11® as the effective oral dose to the skin. Oral and topical dosing variations have been researched and documented by Klausner et.al. (American Association of Pharmaceutical Scientists Nov. 2002 (ref.7)).

The studies reported in this submission varied greatly in duration of treatment. Accordingly, for direct comparison purposes the total dosages used were calculated as

total dose = mg/kg x days dosed for each specimen included (See Table 1). In this manner, it is important to compare studies 7 through 11, in which treatments were with quinic acid analogs calculated to AC-11® equivalents. The result was a high content of AC-11® as quinic acid, ranging from total doses equal to 32,273-75,000 mg/kg (Table 1, studies 7-10). These AC-11® equivalent doses calculated as quinic acid were dramatically higher than the AC-11® doses as reported for the rest of the *in vivo* (rodent) studies,(3-8,22) and the human studies, 12-21 (Table 1, 80-12,000 mg/kg total doses). Yet the observed results were similar. The conclusion that can be drawn from a side by side analysis of the experiments shown in Table 1, studies 7 and 8 is that there are present additional bio-actives in AC-11® other than quinic acid analogs accounting for the increased efficacy observed in AC-11®. Nonetheless, quinic acid analogs (i.e., the QAE) have been identified as one of the primary efficacious ingredients of AC-11®.

The peer reviewed published data involving *in vitro*, rodent and human studies establishes the efficacy of AC-11® containing a minimum 8% Carboxy Alkyl Esters, of which 4% (50% of the active ingredients CAE) are quinic acid analogs – one of the primary bioactive ingredients in AC-11®. In some studies supplemented with either quinic acid or quinic acid ammonium chelate, the total equivalent dose of AC-11® used* was calculated from the quinic acid analog dose used, with AC-11® having 4% QAE content, for direct comparison to the AC-11® supplement doses reported herein. In Table 1, studies 1, 2, 4-9 and 12-21 were supplemented with oral daily doses of AC-11® ranging from 200-700 mg/day (mean = 292 mg/day). Studies 7-10 were supplemented with quinic acid analogs and calculated to the equivalent dose as AC-11® having 4% QAE's. Studies 17-20 were human skin organ culture studies.

Table 1: Studies of AC-11® Doses and Equivalent doses of QA

Study	n	Total Dose AC-11® Used	Clinical Endpoint	Reference
1. In vitro	3-5	100-400 ug/ml (= 100-400 mg/kg)	Cancer cell toxicity	Sheng et al 1998
2. In vitro	2-5	500-1000 ug/ml (= 500-1000 mg/kg)	Cancer cell toxicity, Incr. lymph. survival	Akesson et al 2003B, 2005
3. In vitro	3	$ORAC_{hydro}$* = 885 µmole TE/g $ORAC_{lipo}$ ^ = 11 µmole TE/g $ORAC_{total}$ = 896 µmole TE/g	Scavenger capacity peroxyl radical	Conf. Report #1
4. Rat	5 5	2240 mg/kg 4480 mg/kg	DNA repair stimulation, Immune stimulation	Sheng et al 2000A
5. Rat	12 12	400 mg/kg 800 mg/kg	Reduced DNA damage induced by doxorubicin	Sheng et al 2000B
6. Mouse	7	12,000 mg/kg	Prolong lymphocyte survival	Akesson et al 2003A

7. Mouse	21	Total UV x 77 days =738 J/cm^2 + AC-11 0.5-1.5 % topical = 50-150 g/100 ml or $\geq$ 500mg/kg[c]	UV tumor progression reduced p< 0.02	Conf. report #2 2005[b]
8. Mouse	10	75,000 mg/kg[a]	Increase lymph half-life and inhibit NF-kB	Akesson et al 2005
	24	10,500 mg/kg[c]		
9. Rat	10	720 mg/kg[c]	Recovery of doxorubicin induced DNA damage	Sheng et al 2005
	10	45,000 mg/kg[a]		
	10	45,000 mg/kg[a]		
10. Human	10	1.3 x10^6 mg[a] (=18,571 mg/kg)	Antioxidant and increased tryptophan and nicotinamide levels	Pero et al 2009
	10	2.7 x10^6 mg[a] (= 38,571 mg/kg)		
11. Human	10	2.25 x 10^6 mg[a] (=32,143 mg/kg)	Increased DNA repair and reduced risk from lifestyle	Pero, Lund 2009
12. Human	4	14,700 mg[c] (=210 mg/kg)	Increased levels of WBC	Sheng et al 2001
13. Human	11	42,700 mg[c] (=601 mg/kg)	Increased levels of WBC, reduced decay antibodies	Lamm et al 2001

14. Human	4	14,000 mg[c] (= 200 mg/kg)	Increased DNA repair and increase number of lymph	Sheng et al 2001
	4	19,000 mg/kg[e] (= 271 mg/kg)		
15. Human	5	5600 mg[c] (= 80 mg/kg)[d]	Reduced 8-OH DNA adducts and antioxidant	Pero et al 2005
16. Human	14	7000 mg[c] (= 100 mg/kg)[e]	Reduced 8-OH DNA adducts and antioxidant	Pero et al 2002
17. Human	100[f]	500 mg/kg (= 5 mg/ml in vitro) in vitro topical	Reduced sunburn cells + repair UV T-T dimers	Mammone et al 2006
18. Human	100[f]	500 mg/kg (= 5 mg/ml in vitro) in vitro topical	Enhanced UV repair but no effect on inducing dimers	Emanuel, Scheinfeld 2007
19. Human	300[f]	250 mg/day x 4 days[c] (= 10-25 µg/ml in Vitro) oral skin dose equiv. (total dose = 14.3 mg/kg)	14-42 % reduction in repair of T-T dimers Collagen III over expression	Conf. report #3 2008[b]

20. Human	100[f]	500 mg/kg (= 5 mg/ml in vitro)	21 % reduction T-T dimers	Conf. report #4
	100[f]	1000 mg/kg (=10 mg/ml in vitro)	25% reduction T-T dimers	Conf. report #4
	100[f]	1500 mg/kg (= 13 mg/ml in vitro)	15 % reduction T-T dimers	Conf. report #4
21. Human	34	400mgs/day	Tryptophan and nicotinamide induction via gut pathways.	Pero and Lund 2010
22. Rat	30	160 mgs per kilo/day	Enhanced DNA repair in auditory nerve cells. (OHC)	Guthrie et al 2011

[a]calc. equivalent consumption as AC-11® having 4% QAEs as bioactive but treated with either quinic acid or Quinmax

[b]available from Optigenex upon request

[c]These human studies were supplemented with AC-11® ranging from 200-750 mg/day (mean = 292 mg/day) and then x days of dosing = total dose AC-11®, and in rodents total dose = 40-500mg/kg x days of dosing.

[d]in combination with 3 other nutrients

[e]in combination with 37 other nutrients

[f]number skin cells counted in organ cultures to determine sunburn /normal cells and T-T dimers

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