UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

ORIGINAL

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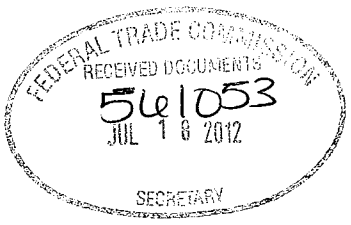

In the Matter of	)	
POM WONDERFUL LLC and ROLL GLOBAL LLC, as successor in interest to Roll International Corporation, companies, and	)	Docket No. 9344
STEWART A. RESNICK, LYNDA RAE RESNICK, and MATTHEW TUPPER, individually and as officers of the companies.	)	PUBLIC

COMPLAINT COUNSEL'S ANSWERING BRIEF TO RESPONDENTS' APPEAL BRIEF

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Dated: July 18, 2012

RECORD REFERENCES

App. – Appendix to Complaint Counsel's Appeal Brief

CCAB – Complaint Counsel's Appeal Brief

CCCL – Complaint Counsel's Proposed Conclusions of Law

CCFF – Complaint Counsel's Proposed Findings of Fact

CX – Complaint Counsel Exhibit

ID – Initial Decision

IDF – Initial Decision Findings of Fact

PX – Respondents' Exhibit

Reply CCFF – Complaint Counsel's Reply to Respondents' Proposed Findings of Fact

Resp'ts Website App. Ex. – Exhibit Listed in Respondents' Website Appendix

RAB – Respondents' Appeal Brief

RPTB – Respondents' Post-Trial Brief

RPTRB – Respondents' Post-Trial Reply Brief

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INTRODUCTION

On appeal, Respondents adopt the same strategy used at trial: obscure the facts and convolute the analysis. Their latest attempt to muddle the record, however, is no more compelling than prior efforts. The relevant questions are straightforward:

- Does the net impression of each challenged ad convey the alleged disease claims?
- Are those claims false and unsubstantiated as charged?
- Are the claims material to consumers' purchase decisions?
- Is the proposed remedy appropriate?

As the record shows, the answer to each question is yes.

Net Impression. Respondents' effort to spin their ads as truthful, modest claims about heart, prostate, and erectile health – and thus unassailable under FTC precedent and protected by the First Amendment – is pure fiction. Rather than confront the interplay of the text and depictions in the ads, Respondents blindly assert that the ads convey only that the POM Products "help promote healthy functioning of various natural processes in the body." (RAB at 26). Respondents' so-called "plain reading" is inconsistent with their own admissions and abundant record evidence that their pitch to consumers has been disease benefit claims. The truth slips out in Respondents' appeal brief, which concedes that "improve prostate and erectile health . . . is really just another way of saying that the POM Products *reduce the risk* of prostate disease and erectile problems." (RAB at 23) (emphasis added). The Commission, utilizing common sense and its own expertise, is well within its authority to determine the ads make the disease benefit claims alleged. Respondents' contention that these virtually express and clearly implied claims are not reasonably conveyed within the context of the ads misses the mark.

Substantiation. Respondents' arguments on substantiation obfuscate the scientific findings and the claims at issue. Just as Respondents feed consumers selective information to convince them that POM's disease benefit claims are backed by $34 million in medical research, they urge the Commission to accept the "totality" of their evidence, as if the evidence might be greater than the sum of its parts. Respondents do not want the Commission to critically evaluate what the science shows and what conclusions relevant experts in the field (including the studies' authors) determine can be fairly drawn from the science, because the parts do not add up to Respondents' claims. Complaint Counsel's experts have reviewed the scientific research for the POM Products, evaluating both the scientific merit of each individual study and the studies in the context of the entire body of relevant evidence. They unanimously conclude that Respondents' science is inadequate to support those claims. And they unanimously conclude that randomized controlled trials (RCTs) would be needed to establish the disease claims Respondents make. In contrast, and quite tellingly, Respondents' experts dodge the substantiation issue by avoiding the product claims, ignoring relevant scientific findings, and evading the limitations of the science.

In Respondents' view, funding preliminary, basic and hypothesis-generating clinical research on their products that sometimes leads to publication in peer-reviewed scientific journals qualifies as "competent and reliable scientific evidence" and gives them license to advertise what Respondent Lynda Resnick characterizes as "amazing" disease benefits. (*See, e.g.*, CCFF¶¶326, 344, 357, 398, 415, 419, 425, 468 (examples of POM ads using strong medical imagery, *e.g.*, picture of POM Juice bottle hooked to an electrocardiogram; use of subscript "x" in POM_x connoting a prescription drug symbol; bold headlines ("Real Studies. Real Results."); and statements touting proven science ("backed by $32 million in medical research")); *see also* CCFF¶570 (Mrs. Resnick stating "what [POM Juice] does for prostate cancer is amazing");

CCFF¶574 (Mrs. Resnick stating "[t]here isn't a man in America that shouldn't drink 8 oz. a day [of POM Juice] because it keeps you from getting prostate cancer or from your PSA from rising. It's really an amazing, amazing thing.")). But, as the two prongs of the substantiation standard suggest, even a published study performed *competently* may not produce results sufficiently *reliable* to support a disease efficacy claim. Respondents understood the study limitations, but chose to ignore them, as evidenced by their 2009 medical research summary and other documents. (CCFF¶966-73, 1010, 1044-54, 1096-1101 (conceding that, *e.g.*, their "current body of [heart disease] research [is] only viewed as '3' on a scale of 1-10 by MDs."; they have no clinical data beyond PSA and "no data on prostate cancer prevention, prior to radiation or prostatectomy.")).

Despite Respondents' efforts in litigation to rewrite their advertising claims and marry them to the science, the record evidence shows, and the ALJ found, that Respondents: 1) represented that the POM Products treat, prevent, or reduce of risk of prostate cancer, heart disease, and erectile dysfunction (ED), and that these benefits are clinically proven; and 2) did not have the level of science experts require to substantiate these disease efficacy and establishment claims. For these reasons, Respondents' assertion that a finding of liability would violate the First Amendment rings hollow. Their claims are false or misleading, and thus fail at *Central Hudson*'s threshold.

Materiality. Although Respondents have refused to admit that the prostate, heart, and ED disease claims at the core of the POM Product marketing campaign are material to consumers' purchasing decisions, their brief acknowledges that "fewer will drink it if the ALJ's ruling is sustained." (RAB at 26). That concession is not surprising. Respondents' entire advertising campaign was geared to tout the POM Products' purportedly extraordinary health benefits –

including their ability to prevent and fight disease. The overwhelming evidence – drawn from Respondents' own internal documents and marketing surveys – compels this conclusion. As the ALJ stated, "it defies credulity to suggest that Respondents would advertise study results related to these conditions if such advertising did not affect consumer behavior." (ID at 295).

Remedy. Respondents' conduct warrants a stringent cease and desist order tailored to the seriousness and deliberateness of their conduct and their ability to readily transfer the unlawful conduct to other pomegranate products and foods they sell. Over the years, Respondents received notice from federal and state regulators, the National Advertising Division of the Better Business Bureau, and members of the scientific community that the disease claims for the POM Products were not supported by the science. Respondents ignored these warnings and continued to carry on as if they were somehow exempt from legal strictures that apply to others.

Perhaps most damning is that Respondents disregarded what their own 2009 Medical Research Portfolio Review disclosed – namely, that they did not have sufficient science to claim that the POM Products treat, prevent, or reduce the risk of prostate cancer, cardiovascular disease, ED, or the other disease conditions they were studying. (CX1029). For example, the "End Game Scenarios" they presented under "Heart Disease" and "Prostate Cancer" each had four possibilities: A) seek FDA botanical drug approval for POM_x for a prevention or treatment claim; B) seek an FDA authorized health claim for POM Juice or POM_x for a reduction of risk claim; C) do "Additional targeted research for Marketing/PR/Medical Outreach purposes"; or D) do "No more clinical research – publicize what we have." (CX1029_0003-04; *see also* CCFF¶¶159, 683, 969-71). In Respondents' view, options A and B were too expensive, carried science risks (*e.g.*, they had "no clinical data beyond PSA"), and may have resulted in a weak health claim that would be of equal value to their competitors. (*Id.*). Options C or D were

clearly advantageous for marketing and, as the record shows, these are the avenues Respondents pursued.

For the reasons stated herein, the Commission should reject Respondents' appeal. As Complaint Counsel urges in its appeal brief, the Commission should set aside the erroneous portions of the Initial Decision and Order and instead enter an injunction consistent with the Notice Order.[1]

ARGUMENT

I. THE RECORD SHOWS THAT THE CHALLENGED ADS ARE DECEPTIVE

A. The Challenged Ads Convey Disease Establishment and Efficacy Claims

The thrust of Respondents' substantive argument[2] on ad interpretation is that the challenged ads do not make express claims of disease prevention, risk reduction, or treatment and, to the extent the ads imply health efficacy, the language is too attenuated to convey the

[1] Complaint Counsel incorporates by reference all relevant facts and arguments raised in its Answering Brief to Respondent Tupper filed July 18, 2012.

[2] Respondents also try to revive myths espoused in their post-trial briefs that: 1) this case involved "an original pool of more than 600" ads; 2) they did not know until recently which of these hundreds of ads Complaint Counsel alleged to be deceptive; and 3) they were hoodwinked into believing that Complaint Counsel was not challenging ads published after December 2008. (RAB at 15, 22; *see also* RPTB at 67 n.17; RPTRB at 5, 181). First, the denominator of 600 ads is merely an invention, presumably aimed at making the universe of objectionable ads look miniscule. Respondents offer no evidence to support this figure, because they cannot. Contrary to Respondents' claim of hundreds, Complaint Counsel identified, and the ALJ recognized, 43 unique challenged ads that exemplify the campaigns used to sell POM Juice and POM_x from 2003 to 2010. (Reply CCFF¶41; ID at 207 ("Complaint Counsel in this case has challenged 43 items")). Second, Respondents knew, upon receipt of the Complaint, the precise claims at issue and a representative sample of the challenged ads. (CX1246). Finally, the ALJ flatly rejected Respondents' claim that ads after December 2008 should be excluded. (ID at 234 n.9 (rejecting Respondents' assertion as "unsupported by the evidence.")). Consequently, Respondents' claim of prejudice is meritless. (RAB at 22).

challenged claims. (RAB at 3, 15, 22-27). But remarkably, they concede that "improve prostate and erectile health" are really just other ways "of saying the POM Products reduce the risk of prostate disease and erectile problems." (RAB at 23).

They contend the ALJ should have distinguished between prevention, treatment, and risk reduction claims and suggest each of these claims calls for "different scientific inquiries and potentially different levels of substantiation." (RAB at 22-23). Respondents fail to ground this assertion in law or evidence.[3] As the Commission recognized in *Thompson Medical*:

> Advertisements do not necessarily convey one message to all persons. One subset of consumers reading an ad may interpret it to contain one message, while another subset may interpret it to contain a different message. Each interpretation is reasonable as long as the subset making it is representative of the group of persons to whom the ad is addressed.

Thompson Med. Co., 104 F.T.C. 648, 789 n.7 (1984), *aff'd,* 791 F.2d 189 (D.C. Cir. 1986); *see also* CCCL¶¶31-32.

For example, when viewing the "Only Antioxidant Rated X" POM_x ad (CX0351/0355), men *with ED* could reasonably understand the message to be that POM Juice and POM_x *treat* ED based in part on the discussion of a study of POM Juice on erectile function "reporting a 50% greater likelihood of improved erections" and stating that the product may assist in the "management of ED." (ID at 229-30). This message is reinforced by the prominent POM_x logo and other language, such as "$32 million in research. We're not just playing doctor." At the same time, healthy men who are concerned about *getting ED* could reasonably conclude from

[3] Respondents failed to introduce any evidence to support their contention that the different claims require different levels of substantiation. Complaint Counsel's experts opined that Respondents' science is inadequate to support any of the challenged claims. (CCFF¶¶963-64, 1037, 1086-87; *see also infra*, Section I.B.2 – I.B.4).

this ad that POM Juice and POM_x *prevent or reduce the risk* of ED. As Respondents admit, and as the ALJ noted, "erectile function and the absence of erectile dysfunction are closely related." (CCFF¶426; RAB at 23; ID at 230). The prevention/risk reduction claims are reinforced by statements such as "Always use protection" and "emerging science suggests that antioxidants are critically important to maintaining good health because they protect you from free radicals, which can damage your body." Likewise, consumers could reasonably interpret this ad to make prostate cancer and heart disease treatment, prevention, and/or risk reduction claims for the POM Products based on the POM_x image, discussion of studies reporting "statistically significant prolongation of PSA doubling times" and decreased "stress-induced ischemia (restricted blood flow to the heart)," and other reinforcing language.

Respondents' advertising was a reflection of the Resnicks' beliefs "that people should try to both prevent and cure diseases as naturally as they can," that pomegranate juice "can be very helpful as a natural disease prevention and curative," including warding off prostate cancer, reducing arterial plaque and factors leading to atherosclerosis, and treating some forms of impotence, and that POM_x has been shown to possess the same health benefits as POM Juice. (CCFF¶¶154, 283-88, 406-12, 574, 576). They used prostate, heart, and erectile "health" as stand-ins for "disease" and, as the record shows, they targeted consumers who were concerned about getting these diseases or who had them. (*E.g.*, CCFF¶¶299-308, 374; ID at 295 (stating that "POM was aware that among those purchasing the POM Products were 'people that have heart disease or prostate cancer in their family, or have a fear of having it themselves'")). Respondents also knew consumers took away those disease messages. (*E.g.*, CCFF¶¶579-96; 616-24).

Respondents argue that the ALJ's facial analysis is contrary to advertising interpretation and logic, because the ads purportedly do not link the POM Products' claimed antioxidant benefit to disease efficacy. (RAB at 23). But the law does not require the Commission to suspend reason and common sense. Respondents' appeal brief mischaracterizes the Commission's authority, under *Thompson Medical* and *Kraft*, to find implied claims absent extrinsic evidence. (RAB at 24).[4] Courts have consistently held that the FTC may use its own reasoned analysis to determine what claims an advertisement conveys. (CCCL¶13). As the Commission acknowledged in *Thompson Medical*, an ad may literally say one thing, but strongly suggest another. *Thompson Med. Co.*, 104 F.T.C. at 789. Contrary to Respondents' assertion, the Commission can "inject something into an ad that is not present" without extrinsic evidence (RAB at 24), assuming the net impression (language and depictions) is clear enough to find an implied claim. *Thompson Med. Co.*, 104 F.T.C. at 789; *see also Kraft*, 970 F.2d at 320 ("[W]hen confronted with claims that are implied, yet conspicuous, extrinsic evidence is unnecessary because common sense and administrative experience provide the Commission with adequate tools to make its findings."); *FTC v. QT, Inc.*, 448 F. Supp. 2d 908, 958 (N.D. Ill. 2006) ("Where implied claims are conspicuous and 'reasonably clear from the face of the advertisements,' extrinsic evidence is not required"), *aff'd*, 512 F.3d 858 (7th Cir. 2008).

[4] Their citation to *United Indus. Corp. v. Clorox Co.* (RAB at 24) is inapposite, because it is a Lanham Act case with a different evidentiary standard for false claims. 140 F.3d 1175, 1178 (8th Cir. 1998). As the Seventh Circuit stated in *Kraft* – which Respondents cite for a different but equally incongruous position (barely imaginable claims) (*see* RAB 24) – courts hearing deceptive advertising claims under the Lanham Act "generally require extrinsic proof that an advertisement conveys an implied claim," but "[c]ourts, including the Supreme Court, have uniformly rejected imposing such a requirement on the FTC." *Kraft, Inc. v. FTC*, 970 F.2d 311, 319 (7th Cir. 1992).

Respondents posit a few faulty syllogisms (*e.g.*, "beef contains protein, protein is essential to life, therefore beef is essential to life") to attempt to illustrate the ALJ's error of logic. (RAB 25). These examples are themselves illogical because, rather than skipping steps in the causation chain or leaving the claim inferred, Respondents' ads clearly led the reader, step-by-step, to the deceptive conclusion. For example, Respondents sold consumers on the following promise: POM Products contain powerful antioxidants, powerful antioxidants prevent or reduce the risk of disease (such as prostate cancer, heart disease, ED, Alzheimer's);[5] therefore, POM Products prevent or reduce the risk of disease. (*E.g.*, CX0016, CX0031, CX0034, CX0103, CX0192, CX0274, CX0314, CX0372, CX0475, CX0120, CX0122, CX0169, CX0180, CX0279, CX0280, CX0328, CX0331, CX0337, CX0342, CX0348, CX0351, CX0013, CX0033, CX0036). Respondents embellished this message with selective quotes from researchers and clinical study results that purportedly showed significant delay of prostate-specific antigen doubling time (PSADT) in men treated for prostate cancer, reduction of arterial plaque in patients with heart disease, and substantial improvement in erectile function in men with ED. Then, they sealed the disease efficacy message with statements like "Science. Not Fiction[,]" "Backed by Science[,]" and "backed by $25 million in medical research." (*E.g.*, CX0274, CX0314_0005, CX0314_0010, CX0372_0003, CX0379_0003-04, CX0475, CX0122, CX0169,

[5] The premise that high levels of antioxidants play a definitive role in preventing or treating disease has not been established. As explained by Complaint Counsel's experts, and conceded by Respondents' expert Dr. Heber, high levels of antioxidants shown in *in vitro* tests may not translate to increased antioxidant levels in the human body. (CCFF¶1104). According to Complaint Counsel's expert Dr. Stampfer, "there is conflicting scientific evidence on the benefits of specific nutrients with antioxidant activity in preventing or treating diseases." (CX1293 (Stampfer, Report at 0011)). He stated that "[a]lthough observational and laboratory studies suggest that these nutrients have beneficial effects, several randomized controlled clinical trials have found no consistent benefit for specific nutrient antioxidants." (CX1293 (Stampfer, Report at 0011); *see also* CCFF¶¶1103-1107).

CX0279). As the ALJ recognized, a few sprinkled qualifying words such as "preliminary," "promising," "encouraging," or "hopeful," does not "materially alter the overall net impression." (ID at 232-33 (referencing IDF¶¶300-01, 312, 333, 342, 349-350, 354, 519)).[6] Respondents conveyed their disease efficacy and establishment claims through savvy marketing that employed virtually express and clearly implied claims to appeal to consumers. As Lynda Resnick states in her guide to marketing, *Rubies in the Orchard*, when it comes to creating messages that resonate, she approaches the task not with a "blunt instrument" but with a "surgeon's scalpel." (CX0001_0019).[7]

Respondents' assertion that their marketing of the POM Products is akin to government agencies making health recommendations or medical centers publicizing results of research is both wrong and beside the point.[8] A fundamental distinction is that Respondents are *commercializing* the POM Products, and advertising disease benefits to further that goal. Respondents have not encouraged consumers to eat pomegranates as part of a diet rich in fruits and vegetables. They have advertised that the POM Products have specific disease-fighting capabilities superior to other antioxidant-rich fruits and beverages, and that those specific disease

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[6] Notably, the Drink to Prostate Health ad they reference (RAB at 14 n.3) uses the word "preliminary" but fails to mention the significant limitations of the study described in the study report, such as "further research is needed to . . . determine whether improvements in such biomarkers (including PSADT) are likely to serve as surrogates for clinical benefit" and lack of a placebo control. (CX0815_0008; *see also* CCFF¶¶986-1001, 1026).

[7] Mrs. Resnick understood the importance of connecting with consumers to evoke interest in the POM Products, remarking that "[i]f we can make you chuckle, we have an opportunity to connect with a more serious message grounded in our brand's identity and extrinsic value." (CCFF¶296; *see also* CCFF¶297).

[8] Many of Respondents' examples identified for this proposition cite evidence that is not in the record. (RAB at 14 n.4; CCRFF¶¶1802-05; 1807-20).

benefits are backed by millions of dollars in medical research. Additionally, unlike Respondents' ads, the sources cited in Respondents' appeal brief candidly acknowledge the limitations of the science.[9]

Consequently, neither a facial analysis nor the record evidence supports Respondents' proffered "plain reading" of the ads. (RAB at 26). If Respondents merely offered POM Juice and POM_x to maintain "healthy functioning of various natural processes in the body," (*id.*) this case would not be before the Commission. Nor are Respondents being held accountable "for all consequent effects" of speculative ad claims (*id.*). This case is about claims that "consumers acting reasonably under the circumstances would interpret" as disease prevention and treatment claims. *Thompson Med. Co.*, 104 F.T.C. at 788. "The purpose of such a requirement is to ensure that the flow of useful, accurate information to consumers will not be deterred by advertisers' fears that they could be held responsible for claims that they could not reasonably have known consumers were going to receive from the ads in question." *Id.* Here, the evidence shows Respondents intended to make the disease claims and knew consumers would take away those claims, *see infra*, Section III, thus they can and should be held responsible for such claims.

B. The ALJ Correctly Found That Respondents' Disease Claims Are Unsubstantiated and False

As explained in Complaint Counsel's appeal brief, competent and reliable scientific evidence for Respondents' treat, prevent, and reduce the risk of disease claims is randomized,

[9] *E.g.*, Resp't Website App. Ex. 9 at 2-3 (NIH states there is "limited evidence to support use of antioxidant supplements to prevent disease."); Resp't Website App. Ex. 22 (Mayo Clinic's Dr. Castle states too early to say if pomegranate juice slows growth of prostate cancer or alters the course of prostate cancer and there is evidence that it affects metabolism of several prescription medications, including blood thinners and some drugs used to treat high blood pressure and high cholesterol).

controlled, clinical trials (RCTs). (CCAB at 21-36). There is no basis in the record, or in precedent, to support a different conclusion. Respondents argue, however, that the ALJ erred in requiring human clinical studies at all, and in finding their claims false and unsubstantiated. In doing so, Respondents obfuscate the claims at issue, as well as the evidence.

1. Well-Controlled Human Clinical Studies Are Required to Provide Competent and Reliable Scientific Evidence for Respondents' Claims

Respondents frame their "basic science" substantiation arguments around imagined, generalized health claims, rather than the challenged claims, which assert a causal link and clinical trials as scientific proof that the POM Products treat, prevent, or reduce the risk of disease in humans. No expert in this case testified that the challenged claims could be substantiated with only "basic science" (*in vitro* and animal studies); in fact, they consistently said the opposite. (deKernion, Tr. at 3063-64 (even strong animal and *in vitro* evidence does not prove an agent works in humans); PX0352 (Goldstein, Dep. at 124) ("you have to study humans to make statements about humans"); PX0025 (Ornish, Report at 0007) (*in vitro* and animal studies have value, but there are limitations in extrapolating to humans)).

For example, Respondents falsely state that their erectile function expert Dr. Burnett "testified that basic science alone" could substantiate "erectile dysfunction health claims," implying that he was referring to the Complaint allegations. (RAB at 30). Rather, Dr. Burnett testified unequivocally that claims to treat ED would require more than *in vitro* and animal studies, and in fact would require RCTs. (Burnett, Tr. 2264 (agreeing that two to three human randomized, controlled were trials needed to conclude that product treats ED); PX0349 (Burnett, Dep. at 57 ("I would have concerns with animal studies or tissue study results being the sole

basis to establish something as a treatment for ED"))).[10] The overwhelming weight of expert evidence, including Respondents' expert evidence, supports the conclusion that "basic science" results must be replicated in humans to provide a basis for the types of claims challenged here. (CCFF¶¶763-64; IDF¶755, 966, 1023-24, 1148).[11] Thus, the ALJ properly rejected Respondents' contentions that basic science alone would suffice, and appropriately considered the human clinical trials, including RCTs, conducted on the POM Products in evaluating the substantiation for the claims at issue.[12]

Respondents argue that the Commission should consider the "totality of the evidence." But their definition of "totality" apparently means *in vitro* and animal studies and only those portions of human studies that seem to support Respondents' position, ignoring other reliable human clinical studies and negative results. (*See* Section I.B.2, I.B.4, *infra* (Respondents ignored negative heart and ED results)). While this selective "standard" would justify Respondents' years of deceptive advertising in this case, there is no basis, other than

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[10] Respondents misleadingly cite previous transcript pages (Burnett, Tr. 2262-63) in which Dr. Burnett discusses interventions that are "likely to improve one's erection physiology[.]" (RAB at 30). But that is not the claim at issue. Respondents fail to cite, let alone address, his subsequent testimony, in which he distinguishes these claims from ED treatment claims.

[11] Indeed, two of Respondents' experts testified that RCTs are the best evidence to support these types of claims. (Goldstein, Tr. 2612-15 (RCTs provide the best evidence of a causal relationship between a nutrient and a disease outcome in humans); CX1339 (Ornish, Dep. at 19-20) (RCTs considered the most rigorous, definitive design, when you are trying to determine whether an intervention is causing an effect)).

[12] Respondents falsely assert that "[n]either side . . . advocated a clinical studies standard" and that the ALJ's ruling requiring clinical studies came "from out of nowhere . . . . [and] has no moorings in the record." (RAB at 29). In fact, Complaint Counsel presented ample expert evidence that human clinical studies (indeed, RCTs) were necessary to substantiate the claims at issue. (CCAB at 21-36).

Respondents' self-interest, to include preliminary basic science but to disregard properly conducted and reliable human clinical trials.

This stance is particularly ironic when, for years, Respondents promoted the POM Products by stating that *in vitro* and animal studies alone are not sufficient, and that they alone, among their competitors, had the human clinical trials needed to back up the specific health benefits of their products. Respondents sponsored multiple human clinical trials, including RCTs, because they recognized the need for strong evidence to support their claims. (CCFF¶¶1119-30). Mrs. Resnick herself noted that "[a]nimal studies are generally a prerequisite for human studies and human studies are considered essential. (We didn't invent this protocol; but *for the science to be considered sound, we had to follow it*)." (CCFF¶1126) (emphasis added). Mr. Tupper also explained that Respondents went "beyond the test tube" to do human clinical research because "[i]t isn't until you see an effect in humans with measurements that are medically meaningful that you know you've got something going on." (CCFF¶1122; *see also* CCFF¶1123 (testifying that POM "pursued a very rigorous approach to science," starting with test tube research, then animal studies, followed by human clinical trials, which are the "gold standard in the scientific research community")).[13] Considered together, the actual totality of the

[13] Respondents argue that RCTs are not required because Complaint Counsel's experts have relied upon non-RCT evidence in entirely different contexts (public health recommendations, cancer surgery, and products not sold to the public). (RAB at 28). Complaint Counsel has already explained that public health recommendations, which are typically based on large long-term human observational trials, and surgical interventions, which are governed by the physician's standard of care, are distinguishable from this case. (CCAB at 27-29; *see also* Stampfer, Tr. 875-79 (observational studies underlying public health recommendations on alcohol involved over a million people over decades)). Moreover, unlike Respondents, Complaint Counsel's experts were not marketing products directly to consumers. (Melman, Tr. 1150-51) (testifying about a product that was still under development and would eventually be submitted to FDA for pre-market approval).

evidence (including RCTs, other human clinical trials, animal and *in vitro* studies) does not support the challenged claims.

2. There Is Substantial Evidence That Respondents' Heart Disease Establishment and Efficacy Claims Are False and Unsubstantiated

The ALJ considered eleven human studies relating to heart disease, but found that none of these studies, alone or in combination, supports the claims that the POM Products treat, prevent, or reduce the risk of heart disease. (IDF¶¶772-947).[14] Respondents focus on a mere handful of studies, but for many reasons, these studies do not constitute competent and reliable scientific evidence for their claims. For example, Respondents rely on the unblinded, uncontrolled Aviram CIMT/BP Study (2004) on a small number of patients with severe heart disease. (RAB at 6). Complaint Counsel's experts testified that it is impossible to tell whether the purported changes in arterial plaque and blood pressure seen were due to pomegranate juice or another factor. (CCFF¶¶814-15).

Respondents also cite the Ornish MP Study (2005) on the effect of POM Juice on myocardial perfusion (blood flow to the heart). (RAB at 6). While showing changes in one measure of blood flow, the study failed to show improvement on two other measures of blood flow or other cardiovascular risk measures. (CCFF¶¶171, 824-54). In any case, change in myocardial perfusion is not a recognized surrogate marker[15] of therapeutic effects on heart disease; improved blood flow will not necessarily result in improved cardiovascular health, such as reduced heart attacks and stroke. (CCFF¶844). It is not clear that the change in blood flow

[14] A summary of Respondents' human clinical heart studies is attached as Appendix A.

[15] A surrogate marker or surrogate endpoint is "a measurement or sign used as a substitute for a clinically meaningful endpoint which measures directly how a patient feels, functions, or survives." (CX1287 (Eastham, Report at 0010); *see also* CCFF¶781).

seen would even be clinically meaningful, because the study did not show that the patients experienced improvement in their clinical symptoms. (CCFF¶849). As Complaint Counsel's expert Dr. Sacks concluded, "the interpretation of [the Ornish MP] study that is most consistent with principles of clinical study design and conduct is that the treatment had no effect on any measure of cardiac health." (CX1291 (Sacks, Report at 0024); CCFF¶854).

Respondents also cite the well-controlled, 289-person Davidson CIMT study (RAB at 6), but focus selectively on two pieces of information: interim results from six months before completion of the study, which ultimately did not bear out at the study's end, and unconfirmed results of an exploratory *post hoc* analysis on a subset of high-risk patients. (CCFF¶¶885-87). They ignore the fact that the study ultimately showed no significant influence of pomegranate juice consumption over placebo on CIMT progression and no statistically significant changes in blood pressure or other tested measures upon its completion at 18 months. (IDF¶¶869-900; CCFF¶882-84).

Despite advocating for the "totality of the evidence," Respondents do not really want the Commission to consider *all* of the evidence. For example, they ignore the 18-month published results of the Davidson CIMT study, as well as two other unpublished studies they sponsored, the Davidson BART/FMD Study and the Ornish CIMT Study, because the results fail to support their claims. Nor do Respondents mention that the Davidson BART/FMD Study, which was conducted on a subset of patients from the Davidson CIMT Study, found no significant differences in blood pressure and other outcomes. (IDF¶¶901-14; CCFF¶¶ 912-19). Similarly,

the 73-patient Ornish CIMT Study, which was blinded and well-controlled, showed no cardiovascular benefit from consuming POM Juice. (IDF¶¶849-68; CCFF¶¶855-68).[16]

These three heart disease studies – the Davidson CIMT Study, the Davidson BART/FMD Study, and the Ornish CIMT Study – were all well-conducted RCTs. (CX1291 (Sacks, Report at 0038)). They showed that, in the study populations, POM Juice provided no statistically or clinically significant benefit for heart disease prevention or treatment, either in direct heart disease endpoints or surrogate endpoints. (CX1291 (Sacks, Report at 0038)).[17] As a result, when the totality of the evidence is taken into account, "there is no competent and reliable evidence to support the conclusion that consumption of [the POM Products] will prevent or reduce the risk of heart disease, or treat heart disease." (CX1291 (Sacks, Report at 0038)).[18]

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[16] *See also* IDF¶¶915-47 and CCFF¶¶920-49 (discussing additional studies with heart disease endpoints that do not support Respondents' heart disease claims). Respondents' repeated failure to address the limitations of their science candidly in their advertising and in this proceeding illustrates why a strong, clear, and precise cease and desist order is needed to ensure their compliance with the law. *See infra* Section IV.

[17] These results are consistent with the totality of the evidence. For example, blood pressure (a valid surrogate endpoint for heart disease) was an endpoint in five of Respondents' RCTs and no benefit was shown in any of these studies. (CX1291 (Sacks, Report at 0013); CCFF¶¶785, 829, 858, 883, 915, 932, 955-58).

[18] Respondents imply that Dr. Sacks testified the POM Products can help treat or prevent disease because "healthy foods (and everyone agrees that the POM Products are healthy) can help treat or prevent heart disease." (RAB at 32). This is another mischaracterization of the record. Dr. Sacks only testified that it is acceptable to emphasize nutrition in treating patients with cardiovascular disease. (PX0361 (Sacks Dep. at 25)). This is not at all the same as saying that a *single product* (*e.g.*, POM Juice) treats or prevents heart disease. Moreover, the POM Products, which have been stripped of the pomegranate fruit's natural Vitamin C and fiber during processing, do not qualify as "healthy." (IDF¶62; PX0268_0003).

3. There is Substantial Evidence That Respondents' Prostate Cancer Disease Establishment and Efficacy Claims Are False and Unsubstantiated

The human prostate cancer studies that Respondents rely upon also fail to support their claims.[19] The Pantuck Phase II Prostate Cancer Study (2006) – evaluating the effect of drinking POM Juice on 46 men previously treated for prostate cancer – is the only published trial examining the effectiveness of POM Juice on prostate cancer in humans. (CCFF¶992). However, the study lacked a placebo-control group and "[w]ithout a control group, it is not possible to conclude that POM Juice alone had an effect on the patients' PSA [prostate-specific antigen]." (CCFF¶¶1002-1007). Dr. Pantuck himself testified that the study's lack of a blinded control group was its greatest limitation. (CCFF¶996).

Furthermore, the study measured "efficacy" via changes in PSADT, which is not recognized by experts in the field as a surrogate endpoint in prostate cancer clinical trials. (CCFF¶978). According to Respondents' own prostate cancer expert, Dr. deKernion, many men with PSA increases after initial therapy do not die of prostate cancer, and altering PSADT has not been shown to change the natural history of the disease by delaying the development of metastases or death from prostate cancer. (deKernion, Tr. 3088-93; CCFF¶¶978, 983). He also acknowledged that "there are no studies that have been performed for sufficient length to determine an impact [of PSADT] on survival" and that "[n]o Phase III randomized trial has been completed to absolutely prove that POM products prolong the life of patients . . . ." (PX0161 (deKernion, Report at 0004, 0011); CCFF¶1038). Indeed, the study's author, Dr. Pantuck, stated

[19] A summary of Respondent's human clinical prostate studies is attached as Appendix B.

that "further research is needed . . . to determine whether improvements in such biomarkers (including PSADT) are likely to serve as surrogates for clinical benefit." (CCFF¶995).[20]

The other prostate cancer study Respondents rely upon, the Carducci dose-response study comparing the effect of taking one POM_x Pill vs. three POM_x Pills daily, has similar weaknesses, in particular the use of a PSADT endpoint and the lack of a placebo group.[21] There was no statistically significant treatment difference (p=.920) in PSADT *between* the groups that took one POM_x Pill vs. three POM_x Pills (*i.e.*, no dose response), suggesting a lack of efficacy. (CCFF¶1025). Furthermore, Dr. Carducci testified that without a placebo, he cannot be sure that any effect on PSADT observed *within* the groups was attributable to POM_x.[22] (CCFF¶1018).

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[20] Respondents knew the problems involved in using PSADT to support prostate cancer claims. Dr. Liker, POM's Medical Director, testified that he became aware that PSADT is not an accepted biomarker for drug approval as early as 2002 or 2003. (CCFF¶1044). In a 2009 medical research summary, Respondents conceded that their PSA-based results would not be accepted if they sought approval for prostate cancer treatment, prevention, or risk reduction claims. (CX1029_0004; CCFF¶¶1045-1046). Indeed, Dr. Pantuck expressed concern, publicly and to Respondents, about using his study to say that POM Juice treats cancer or that all men should be on pomegranate juice to prevent cancer. (CCFF¶¶402-03, 999-1000).

[21] Although the Carducci study design originally included a placebo group, Respondents did not fund the placebo arm, which they conceded was "more of a business decision than a scientific decision[.]" (CCFF¶1016).

[22] Respondents refer to the Carducci study in their appeal brief, and rely on it in large part for their defense, yet provide no cite to the published report, and mischaracterize the results. Although Respondents claim that the study showed "a near doubling of PSADT *from taking POMx Pills* independent of dose," (RAB at 8) (emphasis added), the study report (published in June 2012 in *Prostate Cancer and Prostatic Diseases*, not the *Journal of Clinical Oncology* as Respondents assert, RAB at 7-8), actually states that "no effect of dose was seen, suggesting that the change in PSADT may be due to chance" and that "questions remain as to causality secondary to POMx." (App. B). Moreover, the study's authors, three of whom worked for Respondents, conclude that "[o]nly a placebo-controlled trial could provide the evidence needed to have confidence that the effect was treatment-related." (*Id.*) While not in the record, the report confirms the already substantial record evidence that the POM Products have not been shown to treat prostate cancer.

Therefore, the Pantuck and Carducci studies are not competent and reliable evidence to support a prostate cancer treatment claim for the POM Products.

Nor did Respondents offer any studies of the POM Products in healthy men who do not have prostate cancer. (CX1287 (Eastham, Report at 0016); *see also* CCFF¶¶992, 1010, 1017, 1026, 1030, 1037 (describing Respondents' prostate studies)).[23] Respondents knew they had "no data on prostate cancer prevention, prior to radiation or prostatectomy." (CX1029_0004). Drs. Pantuck and Carducci also testified that the results of their studies do not demonstrate that the POM Products prevent or reduce the risk of prostate cancer. (CCFF¶¶1000, 1018). Thus, the record evidence shows that Respondents lack competent and reliable scientific evidence that the POM Products treat, prevent or reduce the risk of prostate cancer. (IDF¶1143; ID at 282-83).

4. There Is Substantial Evidence that Respondents' Erectile Dysfunction Disease Establishment and Efficacy Claims Are False and Unsubstantiated

Respondents also lack competent and reliable scientific evidence to support claims that the POM Products treat, prevent, and reduce the risk of ED.[24] The primary basis for Respondents' ED claims is the Forest Erectile Dysfunction Study (2007), a double-blind, placebo-controlled study of POM Juice on 53 subjects with mild to moderate ED. (CCFF¶1064-65). Efficacy was assessed using two questionnaires: 1) the Global Assessment Questionnaire (GAQ), an unvalidated questionnaire based on a subject's self-evaluation of whether the treatment had an effect; and 2) the erectile function domain of the International Index of Erectile

[23] At least two other prostate cancer RCTs commissioned by Respondents on the POM Products have been completed, but the results have not been released or published. (CCFF¶¶1026-34).

[24] A summary of Respondents' human clinical ED studies is attached as Appendix C.

Function (IIEF), a validated measure. (CCFF¶¶1058-61, 1066). POM Juice's effect on these two tests was not statistically significant, compared to placebo. (CCFF¶¶1066-69).[25] Respondents acknowledged in internal documents that "the primary endpoints were not met in this trial" and that "the study failed to meet its objectives." (CCFF¶1097).

Dr. Harin Padma-Nathan and Mr. Christopher Forest, the study's co-authors, stated that: 1) the GAQ was not validated for measuring erectile function (CCFF¶1067); 2) the study was underpowered due to Respondents' budget restraints (CCFF¶1071); and 3) the study was only meant as a "pilot" or "proof of concept" study, (CCFF¶1064). They concluded that further studies were needed to confirm any potential benefit for ED, and testified that their study did not demonstrate that POM Juice treats, prevents, or reduces the risk of ED. (CCFF¶1074). This is consistent with the opinion of Complaint Counsel's expert, Dr. Melman. (CCFF¶¶1076-78). Unpublished data from the Davidson BART/FMD Study, which Respondents did not publicize or provide to their erectile function experts, also found no statistically significant difference in IIEF results between the POM Juice and placebo groups. (CCFF¶¶1079-81). Respondents themselves conceded that their ED science was "relatively weak." (CCFF¶1098). Their evidence thus does not support their ED claims. (ID at 288-29).

5. Respondents' Expert Testimony Does Not Support the Challenged Claims

As Complaint Counsel has established, much of the evidence put forward by Respondents is not competent or reliable to support their disease claims, and the studies that *are* competent and reliable do not show that the POM Products treat, prevent, or reduce the risk of

[25] The IIEF erectile function domain results achieved a p value of 0.72, a value which Dr. Burnett agreed is "nowhere near approaching statistical significance." (CCFF¶1076).

disease.[26] Nevertheless, Respondents try to recast the record in a favorable light by arguing that their experts actually testified that the challenged claims were substantiated. Their fanciful reading of the record does not survive even minimal scrutiny.

Respondents imply, for instance, that Dr. Heber testified that the challenged claims for the POM Products were substantiated. (RAB at 11). In support, they claim that he said the POM Products "were likely to cause a significant improvement in cardiovascular health," but he does not say this in the transcript page Respondents cite (Heber, Tr. 2012), or anywhere else in the trial transcript. He did testify that he does not consider nutritional products to be a treatment for disease (Heber, Tr. 2145) and that he was not asked by Respondents whether the POM Products prevent heart disease. (Heber, Tr. 2142-43). Moreover, by his own admission, he is not an expert in heart disease, heart disease treatment, or blood pressure. (CCFF¶728).

Respondents also claim that Dr. Ornish "validated POM's use of basic science [*i.e.*, *in vitro* and animal studies] to support POM's cardiovascular health claims." (RAB at 12). But Dr. Ornish's opinion at trial was based only on the two *human* studies he conducted for Respondents. (Ornish, Tr. 2354-55). He did not opine on the actual challenged claims; he said only that the POM Products are "likely to be beneficial in maintaining cardiovascular health and . . . likely to

[26] Respondents claim that the ALJ held them to a "100% guarantee" standard, requiring them to provide "absolute proof" of efficacy, rather than competent and reliable scientific evidence. (RAB at 30-31). But it is clear from the opinion, which discussed at length the expert evidence presented on Respondents' substantiation, that the ALJ required competent and reliable scientific evidence. (ID at 259-70 (heart disease), 270-83 (prostate cancer), 283-290 (ED)). In doing so, the ALJ pointed out ample facts, summarized above, justifying a finding that Respondents' science was not competent or reliable to support the challenged claims.

help reduce the risk of cardiovascular disease." (PX0025-0005; Ornish, Tr. 2374-75).[27] Thus, Respondents' evidence is irrelevant and was properly outweighed by Complaint Counsel's expert testimony that Respondents' heart disease claims are unsubstantiated.

Respondents also boldly state that they have "more than sufficient" evidence to support claims of treatment and prevention of prostate cancer. (RAB at 32). But their own expert and study authors contradict them. *See* Section I.B.3, *supra*. As the ALJ noted, Dr. deKernion's conclusion that "there was a high degree of probability that the POM products . . . lengthened [PSADT] and, thus may defer deaths from prostate cancer" is not the same as saying the products treat, prevent, or reduce the risk of prostate cancer. (ID at 281-82).[28]

Respondents also rely, again, on Dr. Heber, who is not a prostate cancer treatment expert (CCFF¶728) and never actually opined on the challenged claims. He only testified that the POM Products "lengthen [PSADT] . . . and that those men *may experience a deferred recurrence of the disease or death*" and "are likely to *reduce the risk of prostate problems*" for healthy men. (RAB at 11) (emphasis added). Even if Dr. Heber's opinion matched the challenged claims, his opinion is entitled to little, if any, weight. It contradicts the testimony of not only the expert prostate cancer clinicians called by both sides, but also the prostate cancer study authors, who stated that PSADT has *not* been shown to be associated with delayed recurrence or death

[27] Similarly, Dr. Heber's stated opinion was that the POM Products "have significant health benefits for cardiovascular systems" or "potential health benefits for heart disease," not that the challenged claims were substantiated. (PX0192-0044-45; PX0353 (Heber, Dep. at 76-80)).

[28] Respondents claim that Dr. deKernion opined that PSADT is a valid and effective endpoint for recurrence of and death from prostate cancer (RAB at 12), but their cited evidence (RFF 172, citing deKernion, Tr. 3061) does not support this statement.

(CCFF¶¶983, 994-95), and that there are no studies on the effect of the POM Products in healthy men. (CCFF¶¶992, 1000, 1010, 1018, 1017, 1026, 1030, 1037). The ALJ was justified in crediting the testimony of expert practitioners in the prostate cancer field over Dr. Heber's.[29] Ultimately, substantial evidence supports the conclusion that Respondents' prostate cancer claims are not supported by competent and reliable scientific evidence.

Finally, as Respondents concede, their erectile function experts did not opine on the challenged claims at all. At most, their experts were willing to vouch for POM Juice as "beneficial to erectile health" or providing a "benefit to erectile function." (RAB at 13). But as the ALJ properly noted, in the context of medical science, "erectile *health* is a separate and distinct concept from . . . treatment for the medical condition of erectile *dysfunction*[.]" (ID at 288-89) (emphasis in original). Dr. Goldstein does not recommend POM Juice as a treatment for ED (CCFF¶¶1090, 1093), and Dr. Burnett testified he would be concerned about relying on the Forest ED Study to conclude that POM Juice is efficacious in treating ED. (CCFF¶1088).[30] Nothing in their testimony, or in the record, supports the strong ED claims that Respondents actually made.

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[29] *See also* Kantoff, Tr. 3265 (prostate cancer consultant told Respondents and Dr. Heber at science meeting that while data were encouraging, more work was needed to demonstrate POM's effectiveness).

[30] Respondents state that Dr. Heber (who is not an ED treatment expert, CCFF¶728) testified that "animal studies showed that pomegranate juice markedly improved proper erectile function and would probably do so in humans" and that the Forest ED Study showed significantly improved erectile function. (RAB at 11). But in reality, he testified only that an animal model showed increased blood flow to the penis, and that "in humans, it's much harder to measure that." (Heber, Tr. 1969). He did not testify to any specific conclusion of the Forest ED Study. (Reply CCFF¶135). In any case, "probably improves erectile function" is not a Challenged Claim.

6. The "Prestige" and Expense of Respondents' Science Program Does Not Constitute Competent and Reliable Scientific Evidence for the Challenged Claims

Respondents argue that their science is rigorous enough to support the challenged claims because some of their research has been published or subject to peer review. (RAB at 31). However, the peer review comments and the published studies actually support Complaint Counsel's position that the scientific community would not consider these studies to be competent and reliable scientific evidence for the challenged claims. For example, the Ornish MP Study was rejected by two peer-reviewed journals, because, among other reasons: 1) "[m]ultiple qualified, blinded graders scored this abstract below acceptable range"; and 2) "the study appears very preliminary, with small sample size, apparent baseline imbalances between groups, use of an intermediate endpoint as main outcome measure, and modest differences with large variability." (CCFF¶¶840-41).

Peer reviewers also expressed concern about key aspects of Respondents' other studies, which undermine Respondents' attempts to rely on these results as competent and reliable scientific evidence to support their claims. Dr. Davidson had to revise his manuscript before publication to address peer reviewers' insistence that the results be reported as a negative study "as it is," and to state that he had not conducted any statistical correction for the multiple comparisons run on the subgroup analyses. (CCFF¶¶890-91). Thus, the discussion section of the article, as published, emphasizes the possibility of error and the exploratory nature of the findings, and cautions about interpretation of the subgroup analysis that Respondents now tout as competent and reliable scientific evidence supporting their claims. (CCFF¶887). Dr. Pantuck's prostate cancer study also was published only after he revised his report in response to a peer review comment that the manuscript was "*excessively advocatory* of pomegranate juice as *a*

treatment for prostate cancer." (CCFF¶990) (emphasis added). Finally, a peer reviewer for the *International Journal of Impotence Research* stated that the Forest ED study was "a negative study, not a positive study, and should be presented that way" (CCFF¶1072), and Dr. Padma-Nathan disclosed various limitations of the study in his published report. (CX1193_0003-0004). The peer reviewers' comments are virtually identical to the concerns raised by Complaint Counsel's experts. (CCFF¶¶843-54, 887, 903-11, 1002-04, 1076-77).

Respondents also argue that they have invested more than $35 million in scientific research with prestigious institutions and researchers, resulting in over 100 pomegranate studies (including 17 published human studies), as though this fact in itself constitutes competent and reliable evidence. (RAB at 4). Ultimately, however, Respondents' disease benefit claims must be judged not by the money spent, but by the reliability of the research and, most important, whether there is a "fit" between the research results and their claims. Millions of research dollars,[31] prestigious institutions,[32] and published studies alone do not constitute a reasonable basis, where, as here, the studies are either: 1) not designed and executed in a manner that experts in the field conclude is needed to yield accurate and reliable results for disease treatment and prevention claims; or 2) properly designed and executed, but with negative or inconclusive

[31] Respondents counted a variety of expenses in this $35 million figure, including meeting expenses, exhibition fees and rental expenses, and membership contributions to trade associations, as well as studies on many areas of health that are not at issue in this case or did not show an effect of the POM Products. (CCFF¶¶319-24).

[32] Two research institutions – UCLA (including Dr. Heber) and Technion Institute (including Dr. Aviram) – are responsible for forty percent of Respondents' studies. (Reply CCFF¶268; CX1241). Drs. Heber and Aviram have been on "retainer" as Respondents' scientific consultants since 2003, resulting in payments to them or their institutions in excess of $2.7 million and $4 million, respectively. (CCFF¶¶724, 790).

results. Indeed, Respondents essentially admit that their science does not fit the challenged claims, when they state that their "health research program yielded a series of scientific studies "*suggesting* that POM Juice . . . promotes heart and prostate health and improves erectile function[.]" (RAB at 5) (emphasis added). A "suggestion" that the POM Products promote health is not competent and reliable scientific evidence that the products treat, prevent, or reduce the risk of disease. Stripped of Respondents' misleading "spin," the scientific evidence plainly does not support Respondents' claims.

C. The First Amendment Does Not Protect Respondents' Deceptive Ads

Respondents claim that the challenged ads are protected commercial speech, and thus not actionable, asserting that the ads: 1) are not actually misleading because purportedly there is no evidence anyone was misled, and 2) are not inherently misleading because they "state accurate and verifiable information." (RAB at 17-22). Moreover, while admitting that consumers may not fully comprehend the POM science (RAB at 34), Respondents ironically argue that a finding of liability underestimates consumers' ability to look behind their marketing – which features cherry-picked scientific proof that their products prevent, treat, and reduce the risk of heart disease, prostate cancer, and ED – to ascertain the truth that their products do nothing of the sort. Brandishing Supreme Court cases, Respondents claim that if the Commission were "to sustain the ALJ's liability ruling, the Commission would run head on to the significant constraints that the First Amendment imposes on its FTCA enforcement authority." (RAB at 18). Whether Respondents' goal is to persuade or to intimidate, their arguments are unconvincing.

Respondents' rhetoric neglects a principal tenet of First Amendment jurisprudence: to qualify for constitutional protection, commercial speech must "at least concern lawful activity and not be misleading." *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S.

557, 566 (1980) (establishing familiar four-part inquiry; the threshold question is whether the speech concerns a lawful activity and is not misleading). As the Supreme Court stated in *Virginia Board of Pharmacy*, "[t]he First Amendment . . . does not prohibit the State from insuring that the stream of commercial information flows *cleanly* as well as freely." *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Counsel*, 425 U.S. 748, 771-72 (1976) (emphasis added); *see also id.* at 772 ("[s]ince advertising is the sine qua non of commercial profits, there is little likelihood of its being chilled by proper regulation and foregone entirely. . . . [T]he greater objectivity and hardiness of commercial speech may make it less necessary to tolerate inaccurate statements for fear of silencing the speaker.").

The Initial Decision correctly held that: Respondents disseminated ads and promotional materials making the challenged disease claims; the claims were false and/or unsubstantiated; and the claims were material. (ID at 5-6).[33] Thus, Respondents' claims violate Sections 5 and 12 of the FTC Act, and the claims are entitled to no First Amendment protection. *Bristol-Myers Co. v. FTC*, 738 F.2d 554, 562 (2d Cir. 1984) ("[D]eceptive advertising enjoys no constitutional protection"). As the Commission emphasized recently in *Daniel Chapter One*, "the latter three prongs of the [*Central Hudson*] test are reached if, and only if, Respondent's advertising is not misleading or deceptive. . . . The ALJ found Respondents' commercial speech deceptive . . . Once reaching that finding, no other analysis is necessary." *Daniel Chapter One*, No. 9329, 2009 WL 5160000 at *20 (Dec. 24, 2009), *aff'd*, 405 F. App'x. 505 (D.C. Cir. 2010); *see also FTC v. Nat'l Urological Group*, 645 F. Supp. 2d 1167, 1185 (N.D. Ga. 2008) (rejecting

[33] Record evidence that the ALJ failed to consider likewise supports these conclusions. (*E.g.*, CCAB III.A.4).

defendants' *Central Hudson* arguments and finding whether "advertisements are deceptive, and thus unprotected speech, is a matter that is in the sound discretion of the court."), *aff'd*, 356 F. App'x 358 (11th Cir. 2009).

As Respondents acknowledge (RAB at 19), advertising that is actually misleading or inherently misleading, as opposed to only potentially misleading, is not protected by the First Amendment. Respondents then go on to cite a bevy of Supreme Court cases where, in fact, the advertising was *non-deceptive*, so the issue was what level of government regulation passes constitutional muster for truthful or "potentially misleading" commercial advertising. (RAB at 19-20). But those cases are of no moment. Here, the advertising has been found *actually deceptive* and false under the FTC Act. That finding ends the inquiry.

Undaunted by this precedent, Respondents argue that "actually misleading" under Supreme Court case law requires empirical evidence proving consumers were actually deceived or misled. (RAB 19-20). This argument was squarely rejected by the Commission in *Daniel Chapter One*. 2009 WL 5160000 at *15 (rejecting Respondents' argument that Due Process and the First Amendment required the ALJ to consider extrinsic evidence, and stating, "[f]ederal courts have long held that the Commission has the common sense and expertise to determine what claims, including implied ones, are conveyed in a challenged advertisement, so long as those claims are reasonably clear.") (internal quotations omitted). Indeed, Respondents' citation to *Peel v. Att'y Registration & Disciplinary Comm'n* (RAB at 19-20) incorrectly suggests that the Supreme Court looked to empirical evidence of consumer deception. In fact, it relied on a facial analysis of the ads in question to find that the ads were not actually misleading. *Peel v. Att'y Registration & Disciplinary Comm'n*, 496 U.S. 91, 105-06 (1990) ("The two state courts that have evaluated lawyers' advertisements of their certifications as civil trial specialists by

NBTA have concluded that the statements were *not misleading or deceptive on their face*, and that, under our recent decisions, they were protected by the First Amendment") (emphasis added).[34] Moreover, Respondents' claim that the record contains no evidence that consumers were misled is disingenuous. (RAB at 19-20). That the disease claims were material to consumers – affecting their purchase decision and driving sales of Respondents' POM products – clearly evidences that consumers were misled. (ID at 292-96; *see also* Section II, *infra.*)

Respondents next argue that the claims are not "inherently misleading" because the advertisements contain information that is objectively accurate and verifiable by the consuming public. (RAB at 20-22). Nothing could be further from the truth. For example, between 2004 through at least 2009, Respondents ran ads promoting a 30% reduction in arterial plaque purportedly shown by the small, unblinded Aviram CIMT/BP Study (2004) (*see, e.g.*, CCFF¶¶329-30, 336, 344, 408, 411, 415, 430-31, 435, 437, 443, 449, 454), even after they knew, as early as 2006, of the inconsistent and negative results of the much larger, well-designed, well-controlled Davidson CIMT Study (2009) that showed, at most, a 5% decrease in arterial plaque in some patients measured at an interim point in the study. (*See, e.g.*, CCFF¶420). Even if consumers had the necessary scientific expertise, they would not have been in a position to verify the accuracy or reliability of the Aviram study in relation to the Davidson study, because Respondents delayed publication of the Davidson study for three years while they continued to market POM Juice and POM_x to consumers for this purported cardiovascular benefit.

[34] Indeed, having posited this absurd proposition, Respondents then quickly reverse course by admitting that "the Supreme Court has acknowledged that an advertisement can be adjudged inherently misleading on its face in the absence of consumer survey evidence." (RAB at 20) (citing *In re R.M.J.*, 455 U.S. 191, 205 (1982)).

(CCFF¶¶892-98, 953). Consumers had no way of knowing, when viewing ads stating "Real Studies. Real Results" (*see, e.g.*, CCFF¶468), that they were actually seeing only a selective presentation of the scientific evidence, which ignored relevant negative results. *See, e.g.*, Section I.B.2, *supra.*

Moreover, consumers would have no way to know that when Respondents advertised that the POM Products were "backed by" over $30 million in medical research, the advertisements were referring to expenses that went to exhibition fees, research on conditions not being advertised, and studies that did not show a positive result for the products, among other things. (CCFF¶¶309, 319-24). Contrary to Respondents' contentions, expecting consumers to sift through POM's scientific research to make an independent determination about the accuracy of POM's claims is a far cry from verifying whether an attorney is licensed to practice in a given jurisdiction or holds a certification as advertised. *E.g.*, *Peel,* 496 U.S. at 100-01 (evaluating whether consumers could easily verify Peel's claims of certification as a specialist). Here, Respondents make science-based claims that consumers cannot adequately assess on their own, and that have been found to be deceptive.[35]

The Supreme Court in *Zauderer v. Office of Disciplinary Counsel* recognized that "distinguishing deceptive from nondeceptive advertising in virtually any field of commerce may require resolution of exceedingly complex and technical factual issues and the consideration of nice questions of semantics." 471 U.S. 626, 645 (1985) (referencing FTC deceptive advertising

[35] The attorney cases Respondents claim support their position are also distinguishable from this case, in that the truthfulness of the claims was either not in dispute, stipulated, or established. *See R.M.J.*, 455 U.S. at 205-06; *Peel,* 496 U.S. at 100-01; *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 639-40 (1985); *Ibanez v. Fla. Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 144 (1994).

cases). That is particularly true here, where the products at issue are classic "credence goods." *See generally* Richard A. Posner, *An Economic Approach to the Law of Evidence,* 51 Stan. L. Rev. 1477, 1489 (1999) (defining "credence good" as a good that "the consumer cannot readily determine its quality by inspection or even use, so that he has to take its quality 'on faith.'").

Finally, Respondents complain that by holding them liable for their deceptive claims, the Initial Decision stifles scientific debate about the health benefits of the POM Products. (RAB at 18, 34-35).[36] This is simply not true. The real question is who should bear the burden of verifying complicated scientific information advertised to sell a product or service – the advertiser or the consumer? As noted by Justice Stewart, concurring in *Virginia Board of Pharmacy*:

> [T]he commercial advertiser generally knows the product or service he seeks to sell and is in a position to verify the accuracy of his factual representations before he disseminates them. The advertiser's access to the truth about his product and its price substantially eliminates any danger that governmental regulation of false or misleading price or product advertising will chill accurate and nondeceptive commercial expression.

Va. State Bd. of Pharmacy, 425 U.S. at 777. He later writes, "[i]ndeed, the elimination of false and deceptive claims serves to promote the one facet of commercial price and product advertising that warrants First Amendment protection – its contribution to the flow of accurate and reliable information relevant to public and private decisionmaking." *Id.* at 781.

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[36] In this regard, Respondents' attempt to insert *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) into the debate is unavailing. (RAB at 18, 35). As the Commission recently stated, in *Pearson* "the issue was not condemnation of particular commercial speech found to have been actually misleading, but rather the regulation of broad categories of speech, subject to the latter three prongs of the *Central Hudson* analysis." *Daniel Chapter One*, 2009 WL 5160000 at *20.

For years, Respondents have asked consumers to "Trust in POM" and to believe their presentation of the science. (*See, e.g.*, CX0314_0010). Consumers should not have to play detective to decipher Respondents' claims and determine for themselves that the ads do not truthfully reflect the totality of Respondents' science, which fails to establish a basis for the disease benefits touted. As the record shows, Respondents were well aware of the limits of their science (*e.g.*, CCFF¶966-73, 1010, 1044-54, 1096-1101), but well-qualified, cautionary statements about the reliability of the science or general claims about POM's level of antioxidants do not make for pithy, persuasive advertising copy. Respondents' deceptive and false advertising finds no refuge in the First Amendment.

II. RESPONDENTS' CLAIMS ARE MATERIAL TO CONSUMERS

The ALJ correctly weighed the evidence presented in concluding that the challenged claims are material to consumers. (ID at 290-96). The nature of the claims, Respondents' intent, and evidence that the claims influenced consumers' decisions all show that the challenged claims were important to consumers and likely to affect their choices. *Federal Trade Commission Policy Statement on Deception*, 103 F.T.C. 174, 182-83 (1984) (appended to *Cliffdale Assocs., Inc.*).

First, the advertising claims significantly involve health-related matters, which constitutes strong evidence that the claims were material. *Novartis Corp.*, 127 F.T.C. 580, 687 (1999), *aff'd*, 223 F.3d 783 (D.C. Cir. 2000). Respondents admit that the POM Products' health benefits, including their purported effects on arterial plaque and prostate cancer, are their "unique selling proposition." (CCFF¶¶281-83). "Common sense and experience" support the finding that the challenged health benefit claims, which are the central characteristic of the POM Products, "would be important to consumers considering a purchase and likely affected

consumers' decisions." (ID at 292; *see also* ID at 312 (a "central, and persistent" theme of Respondents' advertising was the POM Products' purported effect on disease and supporting science)).

Second, Respondents made strong health claims and intended to do just that. "An advertiser's intent to make a claim generally implies that the advertiser believes the claim is important to consumers." *Novartis*, 127 F.T.C. at 687. The creative briefs, prepared by POM's marketing team and relied upon by Respondents' in-house ad agency to execute specific ads and campaigns, confirm Respondents' intent. They show that Respondents targeted consumers who were most susceptible to disease benefit claims, namely, consumers who were: 1) "very health-conscious (hypochondriacs)"; 2) seeking a natural "cure" for their current ailments; 3) "men who re scared to get prostate cancer;" and 4) suffering from "ailment[s] that pomegranates have been rumored to help." (CCFF¶¶300, 302-05). Contrary to Respondents' suggestions, these creative briefs were not vague musings of low level employees, but were specific and detailed (by Lynda Resnick's own directive), reviewed by senior level decisionmakers, including Mrs. Resnick and Mr. Tupper, and were the building blocks of Respondents' advertising campaigns. (CCFF¶¶197-99; *see also* ID at 294 (finding argument that creative briefs reflected the opinions of low level employees unpersuasive)).

Respondents' own testimony and documents make clear that they intended to communicate to consumers the very claims challenged here – that the POM Products are efficacious and had been proven by rigorous testing. (CCFF¶¶310-11; *see also* CX0409_0057 (POM_x creative brief stating, "We don't just say our product is great, we have clinical studies that prove its efficacy."); *see generally* CCFF Section V.C (evidence of Respondents' intent)). Indeed, Respondents included medical research in POM Product advertising and marketing

materials precisely because the research made the claims credible and gave consumers a "reason to believe" in the products' benefits. (CCFF¶306). Respondents Lynda and Stewart Resnick testified that they knew that health benefits (for example, that POM "postpones the onset of prostate cancer [and] death") are the primary reason people buy the POM Products. (CCFF¶¶632-33; IDF¶¶1317-18).

Third, there is substantial evidence that Respondents' claims actually affected consumers' choices. Respondents' own marketing surveys, conducted in the ordinary course of business, show that the health claims for the POM Products are material to consumers' purchasing decisions, more so than taste or other reasons. (CCFF¶¶639-50). In one survey, 85% of POM Juice drinkers said they purchased it because it was "healthy/good for my health." (CCFF¶ 641). Among those consumers, "helps promote heart health" (57%), and "helps protect against prostate cancer" (47% of males) were ranked second and third among specific health benefits motivating drinkers of POM Juice. (CCFF¶643). In another online study, long term health was a bigger purchase motivation than taste among heavy pomegranate juice drinkers. (CCFF¶648). They ranked cardiovascular and prostate health as the top two most important health benefits of drinking pomegranate juice. (CCFF¶649). Among a larger population that included drinkers of other juices, 18% of males ranked ED as the first or second most important health benefit to them. (CCFF¶650).[37]

Respondents' own documents also show that including specific information about heart disease and prostate cancer studies in ads increased sales, and that consumers with heart disease

[37] The Commission has relied upon similar consumer survey results as evidence of materiality. *Kraft, Inc.*, 114 F.T.C. 40, 86, 135, 138 n.30 (1991), *aff'd*, 970 F.2d 311 (7th Cir. 1992); *see also Novartis*, 127 F.T.C. at 690.

and prostate cancer, or at risk for such conditions, were in fact buying the POM Products with the expectation that they could treat or prevent those diseases. (CCFF¶¶616-17, 636-37). As the ALJ stated, "it defies credulity to suggest that Respondents would advertise study results related to these conditions if such advertising did not affect consumer behavior." (ID at 295). Moreover, Respondents continued to make the same advertising claims despite being repeatedly warned that they lacked appropriate studies to support the claims (CCFF¶¶662-85), another sign that the claims were material. *Kraft, Inc.*, 970 F.2d at 323, 114 F.T.C. at 137.

In response to this deluge of evidence on materiality (primarily from their own files), Respondents offer one market survey by Dr. Reibstein, which purports to show that few consumers would buy POM Juice based on a belief it cures or prevents a specific disease. But the survey proves nothing about the impact of Respondents' ads. Nor could it: the survey was not based on consumers' review of the challenged ads or claims, it failed to ask follow-up questions to consumers who responded they would buy POM Juice because it is "healthy," and it did not address POM_x ads. (CCFF¶¶ 654, 657-61). Given its many flaws, this survey does not salvage Respondents' immateriality argument. (ID at 295-96).[38] Dr. Reibstein himself testified that, for consumers concerned about heart disease, prostate cancer, or ED, he would expect that the challenged claims would be important to their purchase decisions. (ID at 295; *see also* *Novartis*, 127 F.T.C. at 696 ("[E]ven [Respondent's expert] agrees that a superior efficacy claim

[38] Respondents incorrectly assert that one must show many ad exposures to particular consumers to evidence materiality. (RAB at 37). Complaint Counsel's expert Dr. Mazis testified about the effect of repetition of ads on consumer beliefs (Mazis, Tr. 2752), but he noted that "the impact of advertising on beliefs about a product is not an appropriate measure of materiality[.]" (CX1297 (Mazis, Report at 0009); *see also* Reply CCFF¶¶28, 244).

is likely to affect consumers' purchase decisions.")). Thus, Respondents' survey does not overcome the substantial record evidence of materiality.

Respondents offer no other evidence refuting that the POM Products' advertised effects on disease are material to consumers, who spent over $250 million on POM Juice and POM_x. (CCFF¶139, 143-44). In fact, Respondents acknowledged internally that the promised health benefits were "why [purchasers] put up with the [premium] price." (CCFF¶629). Moreover, they fail to explain why consumers would buy POM_x Pills or Liquid, other than the health claims; taste would clearly not drive sales of the Pills. (*See* CCFF¶303) (creative brief noting that "the pill formula is more medicinal by nature").

Finally, Respondents themselves give away the store by complaining that consumers will not buy the POM Products if they are not allowed to advertise as they please: "Fewer will drink it if the ALJ's ruling is sustained." (RAB at 26). This is the definition of materiality – a claim that influences consumers' purchasing decisions.

III. COMPLAINT COUNSEL'S PROPOSED CEASE AND DESIST ORDER IS WARRANTED

To date, Respondents have been more interested in "hitting [their own] standard" than the standard required by law, when it comes to substantiation for their advertising claims. (S. Resnick, Tr. 1655-56; s*ee also* CCFF Sections VI.E and VI.F). A clear and detailed cease and desist order is essential to ensure that Respondents do not continue to make their own rules. Given Respondents' conduct, Complaint Counsel's proposed order, including fencing-in

provisions covering other products, is appropriately tailored and warranted under the circumstances.[39]

The Commission has "wide discretion" in crafting an appropriate remedy against FTC Act violators. *FTC v. Ruberoid Co.*, 343 U.S. 470, 473 (1952); *see also Jacob Siegel Co. v. FTC*, 327 U.S. 608, 611-13 (1946). The discretion is subject to two constraints: the order must bear a "reasonable relation" to the unlawful practices, *Jacob Siegel*, 327 U.S. at 613, and be sufficiently clear and precise that its requirements can be understood, *Colgate-Palmolive Co. v. FTC*, 380 U.S. 374, 392 (1965). Pursuant to this authority, the courts have affirmed Commission orders requiring diverse, fact-specific remedies. *See, e.g.*, *Sears, Roebuck & Co. v. FTC*, 676 F.2d 385, 389 n.10 (9th Cir. 1982) (requiring competent and reliable scientific evidence for future performance claims for major household appliances); *Thompson Med. Co. v. FTC*, 791 F.2d 189, 192 (D.C. Cir. 1986) (requiring at least two adequate and well-controlled, double-blinded clinical studies for future efficacy claims for a topical analgesic); *Porter & Dietsch, Inc. v. FTC*, 605 F.2d 294, 306-307 (7th Cir. 1979) (mandating disclosure requirements); *Cont'l Wax Co. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (requiring trade name excision). In each instance, the underlying inquiry is the remedy needed to ensure that respondents do not again violate the FTC Act. *See Colgate-Palmolive Co.*, 380 U.S. at 394-95 (noting that the Commission may frame its order broadly enough to prevent respondents from engaging in similar illegal practices). The appropriate scope of relief is based on three key factors: 1) the seriousness and deliberateness of the violations; 2) the ease with which the unlawful conduct can be transferred

[39] For a detailed discussion of the proposed order, *see* Complaint Counsel's Appeal Brief at 37-49 (Section III.C). For a discussion of the proposed remedy with respect to Respondent Tupper, *see* Complaint Counsel's Answering Brief as to Respondent Matthew Tupper's Appeal of the ALJ'S Initial Decision.

to other products; and 3) whether Respondents have a history of past violations. *Thompson Med. Co.*, 104 F.T.C. at 832-33.

The seriousness of these violations is apparent. Respondents engaged in a calculated, years-long effort to promote the POM Products as not only efficacious to treat, prevent, or reduce the risk of disease, but also validated by rigorous human clinical medical research. (*See* CCFF¶¶328, 335, 340, 348, 361, 367, 371, 376, 384, 388, 405, 414, 418, 424, 429, 434, 441, 471, 494, 500, 535, 548, 555, 562, 567, 573, 575, 577). Although their data consisted largely of either unblinded, uncontrolled studies on questionable endpoints (including the Aviram and prostate studies), or RCTs with negative results (the Davidson CIMT, Davidson BART/FMD, and Ornish CIMT studies), they described their research to consumers as "real studies, real results." (*See, e.g.*, CCFF¶¶468, 471) (excerpts from pomwonderful.com website). These claims related to serious diseases, and consumers could not readily judge their truth or falsity. *Schering Corp.*, 118 F.T.C. 1030, 1121 (1991) (Initial Decision) (finding claims "serious" where they "were consciously made despite flaws in the studies relied upon by [the respondent], and because consumers who were not able to assess the validity of those claims relied on the misrepresentation that the [product] had been proven to be effective"). Consumers took to Respondents' message, purchasing more than $250 million of POM Products, in order to reap the disease benefits promised. (CCFF¶¶139, 143-44, 616-17, 629-50).

The deliberateness of the violations is underscored by Respondents' "ready willingness to flout the law[.]" *Sears, Roebuck & Co.*, 676 F.2d at 392. Despite concerns expressed by the New York State Attorney General's Office, the Council of Better Business Bureaus' National Advertising Division, NBC television, Dr. Pantuck, several Investigational Review Boards, the FTC, and the FDA that they were making serious and unsupported disease claims, Respondents

continued to make the same or similar claims. (CCFF¶¶402, 662-84, 686-93). Nothing more clearly evidences this attitude than Respondents' 2009 medical research summary, in which Mr. Tupper recognized that their science was inadequate to make prevent, treat, and reduce the risk of disease claims. (CCFF¶¶966-71, 1045-47, 1096). Even in the face of these warning signs, Respondents were determined to continue marketing the POM Products with these claims. (CCFF¶¶420, 957,1053, 1101).

Moreover, Respondents take no responsibility for the misleading impressions that their advertisements have left on consumers; indeed, they still refuse to brook any criticism of their practices. Mr. Resnick testified that if consumers are taking from Respondents' "Decompress" ad that POM Juice lowers blood pressure, "[i]t's not my problem . . . it's their problem" and that if POM's "ads communicate to consumers that POM can prevent or delay the onset of prostate cancer," he is very comfortable with that claim. (CCFF¶¶618-19). Rather than heed Dr. Pantuck's concern about Respondents' misleading use of his prostate cancer study in their advertising, Mrs. Resnick testified that if she had heard his concern she would have disregarded it because "Dr. Pantuck is not a marketing person." (CCFF¶¶687, 691). And Mr. Tupper testified at trial that Respondents still feel comfortable continuing to advertise the results of the Aviram CIMT/BP Study from 2004 (*i.e.*, 30% reduction in plaque) despite the negative results of the Davidson CIMT Study, which were known since 2006, but which Respondents withheld from publication until 2009. (CCFF¶892-98, 953).

Finally, the violations at issue – misrepresentations of health benefits – are readily transferrable to Respondents' other products. Respondents not only sell other pomegranate-based products, such as POM_x iced coffee, POM_x iced tea, POM_x bars, and a POM sports recovery drink, but also other foods, such as Wonderful Pistachios, Wonderful Almonds, Fiji

Water, and wines. (CCFF¶¶12,123). That they continue in the same or similar line of business means that their conduct could reoccur. *See FTC v. Accusearch Inc.*, 570 F.3d 1187, 1201-02 (10th Cir. 2009) ("[B]ecause Accusearch remained in the 'information brokerage business' it had the capacity to 'engag[e] in similar unfair acts or practices' in the future."). In addition, Respondents have made a variety of health representations – which are not challenged by the Commission's Complaint – about the potential benefits of the POM Products for other health conditions, including but not limited to Alzheimer's, premature aging, and sports recovery. (*See, e.g.*, CCFF¶¶241, 308, 326, 341, 349, 495, 570, 668). Respondents also have researched the health benefits of their other food products, such as the effect of pistachios and Fiji Water on triglycerides and bone health, respectively. (CCFF¶725). The issue is not, as Respondents claim, whether the specific pomegranate *research* is transferable, but whether the unlawful *conduct* (*i.e.*, making false and unsubstantiated health claims) can be replicated with other products. It is clear that Respondents' other products "could be sold utilizing similar techniques"; thus, their violations are transferable and support a multi-product order. (ID at 310-11) (*citing Colgate-Palmolive Co.*, 380 U.S. at 394-95; *Sears, Roebuck & Co.*, 676 F.2d at 392).

Respondents claim that they have stopped the violative conduct and that it is unlikely to reoccur, and therefore, no order is necessary. Complaint Counsel disagrees – indeed, the evidence shows that Respondents continued to make deceptive claims well into 2009 and 2010, more than six years after the first challenged ad. (*See* IDF¶¶290-92 (challenged POM Juice ad from 2003), ¶368, 387 (challenged websites from 2009-2010), ¶321 (challenged POM_x ads from 2010); CCFF¶419 (challenged POM_x ads from 2010)). The record also establishes Respondents' history of mischaracterizing scientific results and ignoring scientific studies in favor of aggressive marketing. (ID at 311) ("This case demonstrates . . . that Respondents' judgment as

to what constitutes advertising 'health benefits' as opposed to what constitutes advertising a scientifically proven effect for disease, has not always been exercised appropriately."). Their conduct is plainly serious, deliberate, and transferable and warrants a clear and specific order covering the POM Products as well as Respondents' other products. Given that Respondents have not changed their attitude toward the violative nature of their advertising claims at all, Complaint Counsel's proposed cease and desist order is necessary to prevent future law violations.

CONCLUSION

For the reasons above, and for the reasons set forth in Complaint Counsel's appeal brief, the Commission should deny Respondents' appeal, grant Complaint Counsel's appeal, and enter the proposed order contained in Complaint Counsel's June 18, 2012 Appeal Brief.

Respectfully Submitted,

Date: July 18, 2012

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CERTIFICATE OF SERVICE

I hereby certify that on July 18, 2012, I filed the foregoing document electronically using the FTC's E-Filing System, which will send notification of such filing to:

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I also certify that on July 18, 2012, I delivered via electronic mail and hand delivery a copy of the foregoing document to:

The Honorable D. Michael Chappell
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Appendix A

Appendix A: Summary of Respondents' Human Heart Studies

Study	Product	Design	Participants	Duration	Results
Aviram ACE/BP (2001) [CCFF ¶¶ 796-804]	Pomegranate Juice concentrate/ no placebo	Unblinded, uncontrolled	10	2 weeks	7 of 10 had statistically significant 36% reduction in ACE activity. 10 had statistically significant 5% reduction in systolic BP (within group analysis).
Aviram CIMT/BP (2004) [CCFF ¶¶ 805-819]	Pomegranate Juice concentrate/ no placebo	Unblinded, uncontrolled	10 drank juice; (additional 9 received no beverage)	1 year	In juice group, 35% decrease in mean CIMT compared to baseline and 12% decrease in systolic BP (within group analysis). In no beverage group, 9% increase in CIMT and no change in BP.
Ornish MP (2005) [CCFF ¶¶ 824-854]	Cardiac Arm Pomegranate Juice/placebo juice	Double blind RCT	45	12 months (failed to complete; results for 3 months only)	At 3 months, significant ($p = 0.05$) improvement in one measure (SDS score) of blood flow as compared to the placebo group, but no significant changes in the other two blood flow measures (SRS and SSS scores). No significant changes in lipids, blood pressure, or markers of oxidative stress and inflammation.
	Carotid Arm Pomegranate Juice/placebo juice	Double blind RCT	17	3 months	No change in CIMT.
Ornish CIMT [CCFF ¶¶ 855-871]	Pomegranate Juice/placebo juice	Double blind RCT	73	12 months	No significant changes between juice and placebo groups for CIMT or elastic properties, systolic and diastolic BP, cholesterol, LDL, HDL, or triglycerides.
Davidson CIMT (2009) [CCFF ¶¶ 879-911]	Pomegranate Juice/placebo juice	Double blind RCT	289	18 months	No significant differences in CIMT between juice and placebo groups. No significant differences between groups in anterior wall and posterior wall values and progression rates, and no statistically significant changes in the measured indicators of inflammation, or oxidative stress (incl. C-reactive protein, PON, and TBARS), or blood pressure.
Davidson BART/FMD [CCFF ¶¶ 912-919]	Pomegranate Juice/placebo juice	Double blind RCT	45	13 weeks	No statistically significant differences between juice and placebo groups in flow mediated dilation, blood pressure, ACE, PON, cholesterol, or TBARS.

Appendix A: Summary of Respondents' Human Heart Studies

Study	Product	Design	Participants	Duration	Results
Denver Overweight (2007) [CCFF ¶¶ 922-926; 940-941]	POMx capsules/ no placebo	Unblinded, uncontrolled	50	28 days	Weight increased and TBARS levels (test of lipid peroxidation in the blood) decreased, but no changes in diastolic and systolic BP or in antioxidant, oxidative, and inflammatory markers (within group analysis).
San Diego Overweight (2007-safety only) [CCFF ¶¶ 929-943]	POMx capsules/ placebo capsules	Double blind RCT	64	4 weeks	No statistically significant changes between juice and placebo groups in blood pressure or any of the antioxidant or inflammation markers, including C-reactive protein and nitric oxide.
Rock Diabetes (2008) [CCFF ¶¶ 944-945]	POMx Liquid and POM Juice/ no placebo	Unblinded, uncontrolled	30	4-6 weeks	Improved PON
Heber/Hill Diabetes (2 studies) [CCFF ¶¶ 946-949]	POM Juice/ placebo juice POMx capsules/ placebo	RCTs	70	12 weeks	No change in PON or malondialdehyde (TBARS)

Appendix B

Appendix B: Summary of Respondents' Human Prostate Studies

Study	Product	Design	Participants	Duration	Results
Pantuck Phase II (2006) [CCFF ¶¶ 986-1012]	Pomegranate Juice/ no placebo	Unblinded, uncontrolled, PSADT endpoint	46	33 months	Average pretreatment PSADT = 15 months; average posttreatment PSADT = 54 months. "[F]urther research is needed to prove the validity of these tests and to determine whether improvements in such biomarkers (including PSADT) are likely to serve as surrogates for clinical benefit."
Carducci Dose Response (2012) [CCFF ¶¶ 1013-1025]	POMx Pills/ no placebo	Double blind, dose response, PSADT endpoint	104	18 months	No significant treatment difference in PSADT between the one capsule and three capsule dose groups. Median PSADT within group went from 11.9 months at baseline to 18.5 months after treatment. "[Q]uestions remain as to causality secondary to POMx."
Pantuck / Radiant (status unknown) [CCFF ¶¶1026-1034]	POMx Liquid/ placebo	Double blind RCT, PSADT endpoint	180	52 weeks	unknown
UCLA/Johns Hopkins/Duke (status unknown) [CCFF ¶¶1026-1034]	POMx Pills/ placebo	Double blind RCT, mechanistic study	70	4 weeks	unknown

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ORIGINAL ARTICLE

A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer

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BACKGROUND: Pomegranate juice has been associated with PSA doubling time (PSADT) elongation in a single-arm phase II trial. This study assesses biological activity of two doses of pomegranate extract (POMx) in men with recurrent prostate cancer, using changes in PSADT as the primary outcome.

METHODS: This randomized, multi-center, double-blind phase II, dose-exploring trial randomized men with a rising PSA and without metastases to receive 1 or 3 g of POMx, stratified by baseline PSADT and Gleason score. Patients (104) were enrolled and treated for up to 18 months. The intent-to-treat (ITT) population was 96% white, with median age 74.5 years and median Gleason score 7. This study was designed to detect a 6-month on-study increase in PSADT from baseline in each arm.

RESULTS: Overall, median PSADT in the ITT population lengthened from 11.9 months at baseline to 18.5 months after treatment ($P<0.001$). PSADT lengthened in the low-dose group from 11.9 to 18.8 months and 12.2 to 17.5 months in the high-dose group, with no significant difference between dose groups ($P=0.554$). PSADT increases >100% of baseline were observed in 43% of patients. Declining PSA levels were observed in 13 patients (13%). In all, 42% of patients discontinued treatment before meeting the protocol-definition of PSA progression, or 18 months, primarily due to a rising PSA. No significant changes occurred in testosterone. Although no clinically significant toxicities were seen, diarrhea was seen in 1.9% and 13.5% of patients in the 1- and 3-g dose groups, respectively.

CONCLUSIONS: POMx treatment was associated with ⩾6 month increases in PSADT in both treatment arms without adverse effects. The significance of this on-study slowing of PSADT remains unclear, reinforcing the need for placebo-controlled studies in this patient population.

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Keywords: pomegranate; PSA recurrence; PSADT

INTRODUCTION

One-third to one-half of patients who undergo primary therapy for localized prostate cancer (PCA) experience rising PSA levels, an early indication of disease recurrence.[1] For these patients, Gleason scores, the time from local therapy to biochemical recurrence and PSA doubling time (PSADT) predict metastasis-free survival and overall survival.[2–4] The Prostate-Specific Antigen Working Group's guidelines on PSADT concluded that clinical evidence supports PSADT as a predictive factor of clinical progression among post-local therapy PCA patients experiencing biochemical recurrence despite questions as to whether PSADT remains consistent over time.[5,6]

PCA patients with PSA recurrence after local therapy, without evidence of metastatic disease, have treatment options that include radiation in the proper setting, androgen deprivation therapy, or observation, with wide variability in applying these treatments. These patients are ideal candidates for trials of treatments with the goal of delaying development of metastatic disease. They are often open to participation in clinical trials of novel agents, in part to avoid the adverse affects of androgen deprivation therapy.[7,8]

In ongoing research, investigators have focused on the antioxidative effects of polyphenols found in soy, green tea and many fruits and vegetables.[9] Preclinical and clinical studies provide evidence of antiproliferative properties of phytochemical-rich foods such as pomegranate juice.[10] The ellagitannins in pomegranate juice have demonstrated anti-tumor activity *in vitro* and *in vivo* in human PCA cells through downregulation of NF-kB, cyclin-dependent kinases 2/4/6 and Bcl-2 and upregulation of p21/WAF1.[11–14] Recent research demonstrated that pomegranate extract (POMx) also inhibits Akt and mTOR phosphorylation in PCA cells.[15]

In 2006, Pantuck *et al.*[16] published results of a 2-year, phase II clinical trial of pomegranate juice (eight ounces) in PCA patients

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with a rising PSA after surgery or radiotherapy. Mean PSADT increased from 15.6 months at baseline to 54.7 months following 33 months of therapy.[16] Our study explores a similar end point in a more inclusive biochemical recurrence population, uses POMx capsules instead of juice, and assesses dose response. This randomized, double-blind trial investigates the effects of two doses of POMx on PSADT over 18 months in men with a rising PSA after local therapy. We also report on tolerability and toxicity, compare PSA objective response (≥50% reduction in PSA) between dose groups and assess study compliance.

MATERIALS AND METHODS

Study participants

Study participants were recruited from the medical oncology practice at the Kimmel Comprehensive Cancer Center at Johns Hopkins and from six private urology clinics throughout the US. Participants had histologically confirmed adenocarcinoma of the prostate and had undergone radical prostatectomy or external beam radiation therapy, cryotherapy and/or brachytherapy. Patients were experiencing biochemical recurrence, defined as a rising PSA on ≥3 time points at least a month apart, within 1 year prior to enrollment, and had no radiographic evidence of metastases. Patients with positive lymph nodes on surgical pathology, who were subsequently found to be radiographically free of metastases were allowed on study. Men treated with radical prostatectomy or multiple therapies such as surgery plus radiation were required to have a PSA $\geq 0.4\,ng\,ml^{-1}$. Primary radiation therapy or cryotherapy patients were required to have a PSA $>1.5\,ng\,ml^{-1}$. Men treated with neoadjuvant hormonal therapy along with external beam radiation were required to have a PSA greater than the nadir plus $2\,ng\,ml^{-1}$. There was no upper limit of PSA levels or Gleason score. Men who had therapies that modulate testosterone levels within 1 year prior to the first dose of study medication were excluded, as were patients undergoing concomitant treatment with experimental drugs, high-dose steroids or any other cancer treatment within 4 weeks prior to the first dose of the study product. Participants were included only if they agreed to abstain from commercially available pomegranate products and maintain other dietary supplements at their current dose during the study. Men were excluded if they had Eastern Cooperative Oncology Group performance status >2 or uncontrolled intercurrent illness that limited study compliance. Men were also excluded if they had testosterone $<1.5\,ng\,ml^{-1}$, white blood cell <3000, absolute neutrophil count <1500, platelet count <100 000, creatinine level >2.5 times upper limit of normal, serum alanine transaminase and aspartate aminotransferase >2.5 times upper limit of normal and/or total bilirubin outside normal limits.

Study design

The study was an 18-month, multi-center, randomized, double-blinded, two-dose trial, powered to detect a 6-month increase in PSADT in an evaluable study population of 80 patients. Participants were stratified by the subject's initial PSADT (≤9 or >9 months) and their Gleason score (≤6 or 3+4 and 4+3 or ≥8). The Gleason score was collected at the time of biopsy for radiation patients and prostatectomy for surgical patients. At initial screening, participants underwent medical history and physical examination, pathology review, complete blood count, clinical chemistry panel, fasting lipid panel, urinalysis, concomitant medication assessment, tumor evaluation and measurement of Eastern Cooperative Oncology Group performance status, serum PSA, testosterone, estradiol, sex-hormone-binding globulin, dehydroepiandrosterone, insulin growth factor and androstenedione. Patients were randomly assigned to receive daily dosing of two placebo –plus one capsule of POMx or three capsules of POMx, a pomegranate, *Punica granatum* L, wonderful variety extract. Each POMx capsule contains 1000 mg of polyphenol extract, comparable to about 8 oz of pomegranate juice. Serum PSA, hormones, other chemical and hematological/laboratory assessments, diet (questionnaire), compliance (diary) and adverse events (interview) were measured quarterly.

The protocol was approved by the institutional review boards at Johns Hopkins and a central institutional review board for each participating site. Each participant gave written informed consent. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v3.0) defined toxicity severity grades. The protocol called for removal of any subject with grade 4 toxicity and delay of therapy for subjects with grade 3 toxicity ≥2 weeks. When grade 2 toxicities occurred, the investigator had the option to continue treatment with careful monitoring or withhold treatment until the values returned to grade ≤1. Other reasons for patient removal include disease progression, withdrawal of consent, non-compliance and investigator judgment.

Study outcomes

The primary objective was to define the effect of two different daily doses of POMx (one or three capsules) on PSADT over 18 months. PSADT computation used the natural log of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA on time (months). All the available PSA measurements in the year prior to patient enrollment were used to calculate baseline pretreatment PSADT. The post-baseline PSADT was calculated using PSA measurements obtained at baseline and every 3 months during treatment. Patients with no on-study PSA measurements were excluded from the analysis of primary outcome.

A secondary objective was to compare PSA objective response rates, progressive disease rates and stable disease rates between the two arms. Objective PSA response was defined as a decrease of ≥50% in the PSA compared with baseline level, confirmed 6 weeks later. Progressive disease, defined by PSA changes, for patients who achieved ≥50% decline in PSA was defined as an increase in PSA ≥50% over the nadir after at least 6 months on study, confirmed at least 2 weeks later, and minimum PSA rise was $>5\,ng\,dl^{-1}$ or back to pretreatment baseline. For subjects whose PSA had not decreased by 50%, progressive disease was defined as an increase in PSA value ≥50% of baseline or PSA nadir, whichever was lowest, after at least 6 months of treatment, confirmed at least 2 weeks later with a change $\geq 5\,ng\,dl^{-1}$. Stable disease response was defined as any response that did not qualify as objective response or progressive disease.

Progressive disease was also defined as the appearance of radiographically evident metastatic disease and/or physical symptoms felt to be cancer related. In addition, patients not meeting protocol-defined PSA progression came off study upon mutual agreement of physician and patient that progression had occurred. Most commonly, PSA progression was defined with a PSA increase <5 ng/dl (that is, non-protocol defined progression). These patients were not eligible for the open-label extension study.

Statistical analyses

We hypothesized that a paired *t*-test with 80 evaluable patients would yield 94% power to detect a 6-month increase in PSADT from baseline with a s.d. of 15 months. In terms of choosing a more effective daily dose, 40 subjects in each dose group would provide >80% power to detect a 10-month difference in PSADT at a two-sided alpha level of 0.05, also assuming a 15-month s.d.. The target accrual was 100 participants allowing for a dropout rate of 20% to meet the accrual objective of 80 evaluable patients.

A Wilcoxon matched-pairs signed-ranks test and paired *t*-test were used to assess the difference of PSADT on study compared with the baseline for both dose groups combined. The nonparametric test was the primary analysis because the distribution for change in PSADT is highly skewed (non-Gaussian). The change from baseline in PSADT between the two groups was compared using the Wilcoxon rank sum test and the two sample *t*-test.

PSADT was categorized as: (a) <3 months, (b) 3–8.9 months, (c) 9–14.9 months, (d) >15 months or (e) negative slope (that is, decreasing PSA). A shift table showed the number and percentage of subjects with PSADT in each category for baseline and post-baseline PSADT for each treatment group.

Subjects with a negative baseline PSADT (decreasing PSA) were excluded from the analysis of change from baseline to post-baseline PSADT. As has been done previously, subjects with a negative post-baseline PSADT were assigned the largest positive PSADT observed in the

study (1532 months), allowing those patients to be included in the intent-to-treat (ITT) analysis.[3]

RESULTS

Participant characteristics

Between October 2007 and December 2008, 104 patients were enrolled and randomly assigned to low- and high-dose POMx groups. May 2010 was 18 months after the last patient enrolled, and data was gathered and the blind was broken in August 2010. Three patients who had no post-baseline PSA measurements were excluded, leaving 101 patients in the ITT. Our analysis is concluded on a modified ITT patient population consisting of 95 patients (46 low and 49 high dose), excluding 6 patients who had declining baseline PSA values (negative PSADT) at baseline. Two additional patients whose PSA did not meet minimum values and one patient taking prohibited medications were excluded from the modified ITT analysis, leaving 92 patients in the evaluable population (45 low and 47 high dose). Age, prior local therapy, Gleason Score, PSADT and other baseline characteristics were similar between the two dose groups (Table 1). Median baseline PSADT was 11.9 and 12.2 for the low- and high-dose groups, respectively.

Table 1. Participant characteristics

Characteristic	*Double-blind treatment*			
	1 POMx, n=50	*%*	*3 POMx, n=51*	*%*
Age (years)				
Mean	71.8		73.5	
Range	51–89		54–92	
Race				
African American	1	2.0%	3	5.9%
White	49	98.0%	48	94.1%
Gleason total score				
Mean	6.4		6.5	
s.d.	1.2		0.9	
Median	7		7	
Range	4–10		4–8	
Baseline PSADT				
⩽9 months	14	28.0%	19	37.3%
>9 months	36	72.0%	32	62.7%
Mean	15.1		14.4	
s.d.	12.9		9.5	
Median	11.9		12.2	
Gleason score				
⩽6 or 3+4	38	76.0%	38	74.5%
4+3 or ⩾8	12	24.0%	13	25.5%
Prior therapies				
Surgery	30	60.0%	22	43.1%
Surgery with radiation	6	12.0%	6	11.8%
Cryotherapy	0	0.0%	2	3.9%
Radiation therapy (XRT)	27	54.0%	27	52.9%
Brachytherapy	9	18.0%	10	19.6%
Anti-androgen deprivation therapy (ADT) with XRT	6	12.0%	7	13.7%
ADT without XRT	5	10.0%	10	19.6%

Abbreviations: POMx, pomegranate extract; PSADT, PSA doubling time.

PSA and PSADT outcomes

The primary end point, median PSADT, for the modified ITT participants increased from 11.9 to 18.5 months ($P<0.001$) with no significant difference between the arms ($P=0.554$). Median PSADT for patients in the low-dose group increased from 11.9 to 18.8 months ($P<0.001$) and from 12.2 to 17.5 months ($P<0.001$) in the high-dose arm (Table 2).

Objective PSA declines meeting response criterion was seen in 1 out of 46 patients in the low-dose arm and 1 out of 49 patients in the high-dose arm (Table 3). Stable disease was seen in 36 patients (78%) in the low-dose arm and 40 patients (82%) in the high-dose arm. Protocol-defined progressive disease was seen in 9 patients (20%) in the low-dose arm and 8 patients (16%) in the high-dose arm. Despite the low level of objective response, six patients in the low-dose arm and nine patients in the high-dose arm experienced declining post-baseline PSA values.

Figure 1 illustrates the percentage changes in PSADT for the 1- and 3-POMx patient groups using a waterfall plot. In the 1-POMx group, 76% of patients had stable or lengthening PSADT and 46% had ⩾100% increase in PSADT. In the 3-POMx group, 82% of patients had stable or lengthening PSADT and 41% had ⩾100% increase in PSADT.

Figure 2 illustrates the distribution of patient response by baseline PSADT range. The majority of patients showed movement to slower PSADT ranges: 75% of patients with PSADT <3 months, 61% of patients with PSADT 3 to <9 months and 81% of patients with PSADT 9 to <15 months. In all, 14 patients (14.7%) moved to a faster PSADT range.

Table 2. PSADT by treatment group at baseline and post baseline

Treatment	*Baseline PSADT (months)*	*Post-baseline PSADT (months)*	*P*
1 POMx	11.9	18.8	<0.001
3 POMx	12.2	17.5	<0.001
Total	11.9	18.5	<0.001

Abbreviations: POMx, pomegranate extract; PSADT, PSA doubling time.

Compliance

A total of 92% of patients completed 6 months, 70% completed 12 months, and 36% completed 18 months on treatment, with no significant difference between the two dose groups. In all, 58% of patients (60 patients) completed the double-blind treatment (either completing 18 months or meeting the protocol-defined progression). In all, 42% discontinued treatment before reaching the defined guidelines for discontinuation. One-third of the patients who discontinued before 12 months met the protocol definition of PSA progression. The most frequent reasons reported for premature discontinuation were non-protocol-defined PSA progression/investigator judgment (15 patients), withdrawn consent (9 patients of whom 6 experienced PSA progression), study-related diarrhea (3 patients) and protocol non-compliance (3 patients). Investigators occasionally reported multiple reasons for discontinuation.

Adverse events

There were no deaths or drug-related serious adverse events reported among the patients. A total of 18 patients had drug-related adverse events, of which 12 were gastrointestinal. diarrhea of grade ⩽ 2 was reported in 8 patients (7.7% of total, 1.9% in 1 POMx and 13.5% in 3-POMx) and deemed drug-related in only 5 patients (all 3-POMx). One patient in the 1-POMx group experienced reflux disease and six patients in the 3-POMx group experienced other study-related gastrointestinal adverse events including nausea (four patients) and abdominal pain, constipation, frequent bowel movements, stomach discomfort and vomiting (one patient each). No grade 3–4 clinical chemistry, hematologic or hormonal toxicities were reported. Ten patients experienced

Table 3. PSA response >18 months of trial

Treatment	*Objective response≥50% PSA reduction*	*Stable disease*	*Progressive disease*
1 POMx (95% CI)	1/46 (2%) (0.5–11.5%)	36/46 (78%) (63.6–89.1%)	9/46 (20%) (9.4–33.9%)
3 POMx (95% CI)	1/49 (2%) (0.5–10.9%)	40/49 (82%) (68.0–91.2%)	8/49 (16%) (7.3–29.7%)
Total (95% CI)	2/95 (2%) (0.7–7.4%)	76/95 (80%) (70.5–87.5%)	17/95 (18%) (10.8–27.1%)

Abbreviations: CI, confidence interval; POMx, pomegranate extract.

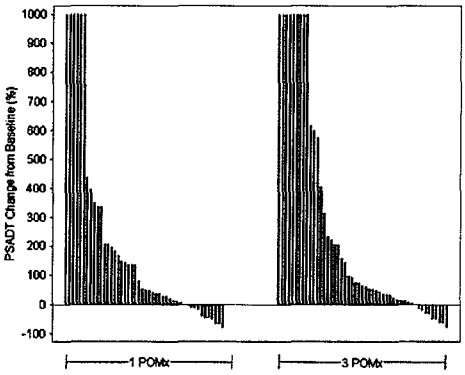

Figure 1. PSADT percentage change from baseline for each patient in the 1-POMx and 3-POMx treatment groups. (Notes: (1) Patients with negative baseline PSADT were excluded, (2) Patients with negative post-baseline PSADT were assigned the largest observed post-baseline PSADT and (3) Six 1-POMx and nine 3-POMx subjects had PSADT percentage change from baseline >1000%). POMx, pomegranate extract; PSADT, PSA doubling time.

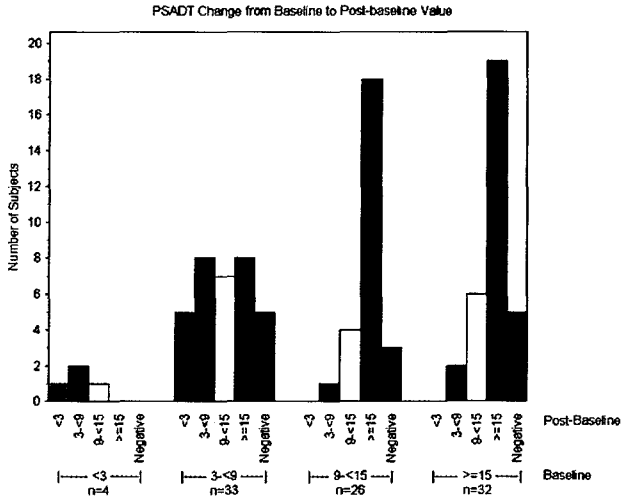

Figure 2. Number of subjects in each post-baseline PSA doubling time (PSADT) range grouped by baseline PSADT range.

cardiac-related adverse events (three in 1-POMx and seven in 3-POMx) such as angina pectoris, arrhythmia and congestive heart failure. None were considered study-drug related; most had been diagnosed with cardiac conditions prior to randomization.

No significant changes were seen in testosterone. Estradiol trended higher in the high-dose group from 28.0 to 32.3 pg ml^{-1}, but not in the low-dose group. The changes in estradiol ranged widely from −37.45 to +38.43 pg ml^{-1} in the low-dose group and from −25.84 to +30.41 pg ml^{-1} in the high-dose group. sex-hormone-binding globulin increased in both groups (42.5–54.7 nmoles l^{-1} in 3-POMx group and 42.8–49.2 nmoles l^{-1} in 1-POMx) with no significant difference between groups.

DISCUSSION

This randomized, phase II, double-blind, dose-finding study compared the effects of two dose levels of POMx on PSA kinetics in men with a rising PSA following radiation or radical prostatectomy. The study met its primary objective as hypothesized, with a lengthening of PSADT ≥6 months (11.9–18.5 months, $P=0.001$), with no significant difference between dose groups. PSADT increases were noted by patients across the range of baseline PSADT values, although shortening of PSADT was recorded in 20 (19.8%) patients, as might be expected with a broad patient population. In clinically reviewing patients with shortening of PSADT, none experienced clinical harm. Several transitioned to subsequent treatments and accounted for early withdrawal, moving primarily to androgen deprivation therapy.

The study accrued quickly, in part because patients were disposed to forgo androgen deprivation therapy therapy to avoid associated toxicities.[7,8] The majority of patients stayed on treatment per protocol, but 42% of patients left prematurely over the 18-month study. Patients who left early showed evidence of PSA progression, but often did not meet the protocol definition of a rise of 5 ng dl^{-1}, after 6 months on treatment. Premature departure of patients often reflected investigator and/or patient anxiety concerning disease progression due to rising PSA values, however, 70% of patients remained on study for a year providing adequate on-study PSA values to calculate PSADT reliably. A total of 28 patients in the low-dose arm and 27 patients in the high-dose arm entered the high-dose, open-label extension study and 37 patients remained on study after 18 months of treatment in the open-label extension. Only 8% of patients left the study prior to completing 6 months, and nearly 60% completed protocol, as planned. This level of completion of the 18-month protocol reflects a disease that continues to progress, and PSA increases can be concerning. When progression occurs, patients frequently ask for access to treatments that could result in a decrease in PSA. Researchers may want to consider shorter trial duration in future studies in this patient population.

These observations of lengthening of PSADT in patients treated with POMx are consistent with the results of the Pantuck *et al.*[16] study of pomegranate juice in a more narrowly defined patient population (0.2<PSA<5 ng ml^{-1}, Gleason score ≤7). At 24 months of treatment, the change from median baseline PSADT to median post-baseline PSADT was 11.5–19.9 versus 11.9– 18.5 months at 18 months treatment in our study. Pantuck's patients were more homogenous and had baseline PSAs ≤5 ng ml^{-1}, whereas 31% of patients in our study had baseline PSA levels >5 ng ml^{-1}, ranging up to 32 ng ml^{-1}. The percentage of patients who had a decreasing PSA on study was roughly similar (18% for Pantuck and 13% in our study). Pantuck's analytical methodology excluded subjects with negative post-baseline PSADT from analysis, thereby underestimating the reported effects. We included any patient with on-study PSA measurements and those coming off quickly may have led to over- or underestimates of the

effects of POMx on PSADT. To enable inclusion of all subjects in the ITT population and avoid underestimating the median, we included patients with declining PSA values by converting their negative PSADT to the highest PSADT experienced by study participants, as was done in previous trials.[3,17]

The lack of dose response requires discussion because it may imply that changes in PSADT were not brought about by the compound. An alternative explanation is that the lower dose was sufficient and the higher dose exceeded a threshold for 'drug' activity. Such a result is not uncommon in the use of dietary supplements where dose-limiting toxicities are not found.[18,19] The higher rate of diarrhea in the high-dose group suggests the possibility of reduced absorption and if true, would correlate with decreased bioavailability. However, we did not measure pharmacokinetics and only 13% of patients in the high-dose group had diarrhea. Therefore, dose-ranging studies like this could benefit from evaluation of bioavailability with markers such as urolithin A, which has been found to be present in urine 24 h after administration of pomegranate juice.[20]

The major limitation of our study is the lack of a placebo arm. A placebo arm was considered, but given the perceived positivity of pomegranate juice, a placebo control was felt to pose difficulties for patient accrual. A dose-response study was an alternative. The US Food and Drug Administration describes dose-response studies as 'one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness' consistent with Code of Federal Regulations Title 21, Section 314.126.[21] In this study, no effect of dose was seen, suggesting that the change in PSADT may be due to chance. Only a placebo-controlled trial could provide the evidence needed to have confidence that the effect was treatment-related. In three prior trials in similar patient populations, patients on the placebo arms experienced substantial lengthening of PSADT while on study. In a Rosiglitazone trial involving 106 patients, 73% of patients on placebo had an increase of PSADT in excess of 100%, and 31% exceeded 200% in PSADT lengthening.[22] In an Atrasentan trial involving 222 patients, 78% of the patients on placebo had a lengthening of PSADT.[23] In a celecoxib trial involving 78 patients, 20% of the patients on placebo had $>200\%$ increase of PSADT.[24] In our study, 46% of the low-dose and 41% of the high-dose group showed PSADT increases $\geqslant 100\%$, and 28% and 37%, respectively, exceeded 200%. The high levels of PSADT lengthening seen in placebo arms of prior studies along with the lack of a significant dose-related effect in our study raise the question whether these results could be due to statistical variation and/or placebo effect. Though our study was positive as designed, our results do not definitively show that changes in PSADT can be related to POMx administration. The lack of dose effect that we hypothesized suggests that future studies should be placebo-controlled and use of low-dose POMx appears appropriate. A phase III, 180 patient, placebo-controlled, 2:1 randomized study of POM juice is maturing (NCT00732043). In addition, a randomized, placebo-controlled, pre-surgical phase II trial involving 70 patients will measure the effects of POMx consumption on oxidative damage, proliferation and localization of urolithins in prostate tissue (NCT00719030).

Variations in measurement of PSA values may contribute to variability in results. Baseline PSADT values were calculated using PSA levels collected at irregular intervals $\geqslant 1$ month apart within the year prior to study initiation using site-specific laboratories; on-study measurements were obtained consistently every 3 months using a central laboratory. A period of rigorous measurement of PSA values, using a central laboratory, prior to randomization may enable more accurate assessment of baseline PSADT. Further investigation is warranted to illuminate statistical variability in PSA measurement and the placebo effect in trials of therapeutic agents in this patient population.

A related issue is whether changes in PSADT are acceptable end points for clinical trials. Retrospective studies have shown that PSADT is a strong predictor of metastasis-free survival[25] and overall survival[3,26] or both.[4] However, prospective studies are needed to provide confirmation that PSA declines accompanying drug administration correspond with improved metastasis-free survival and overall survival.

No significant changes were seen in testosterone levels, and although significant increases were seen in estradiol in the high-dose group, there was high variability in the measurements. Plants such as pomegranate, which contain phytoestrogens, may raise estrogen levels and theoretically could cause clinically significant estrogenic effects. In this study, estradiol levels fluctuated, sometimes rising just above the reference upper limit of $50\,pg\,ml^{-1}$ and subsequently declining while still on study, suggesting that the fluctuations were unrelated to the study compound.[27] No clinically significant estrogen-related side effects, such as breast enlargement, were reported. In addition, no significant difference in change in PSADT was seen between the low- and high-dose POMx groups, despite the measurably different increase in estradiol in the high-dose POMx group. In other words, changes in PSADT do not seem to be affected by increases in estradiol. However, given the small sample size, estradiol should be monitored in future studies of POMx.

This randomized, double-blind, dose-finding study in PCA patients with rising PSA attempted to rigorously examine a widely consumed natural product under an Investigational New Drug Application. PSADT lengthened in men on this study, independent of dose level without adverse effects, but questions remain as to causality secondary to POMx. This study confirms the need for placebo-controlled trials when assessing PSADT and ultimately for using clinically meaningful end points such as metastasis-free survival and overall survival before recommending the use of POMx by PCA patients.

CONFLICT OF INTEREST

The corresponding author, Michael Carducci, received $1500 in 2007 from POM Wonderful, LLC, for participating in a discussion of future trials. Harley Liker and Patricia Wozniak are consultants to POM Wonderful, LLC, and Brad Gillespie was, until 2011, the vice president of POM Wonderful. The remaining authors declare no conflict of interest.

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Appendix C

Appendix C: Summary of Respondents' Human Erectile Dysfunction Studies

Study	Product	Design	Participants	Duration	Results
Forest ED Study (2007) [CCFF ¶¶ 1063-1078]	Pomegranate Juice/ placebo	Double blind RCT, GAQ and IIEF endpoints	53	10 weeks (two 4-week treatment periods and one 2-week washout period)	Neither the GAQ nor the IIEF erectile function domain had statistically significant results.
Davidson IIEF Study [CCFF ¶¶1079-1081]	Pomegranate Juice/ placebo	Double blind RCT, IIEF endpoint	27	13 weeks	IIEF erectile function domain results were not statistically significant.