CEBP Focus: Tobacco Research

Review

Methods Used in Internal Industry Clinical Trials to Assess Tobacco Risk Reduction

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Abstract

Objective: **Methods to assess reduced exposure products should include those that aid in determining likely patterns of human use and exposure. Tobacco industry clinical trial methods may provide insight into strategies to assess potential reduced exposure products (PREP) for public health purposes. Internal tobacco industry documents detailing human clinical research with PREPs were examined to document major research strategies used and identify potentially fruitful methods not currently used in the mainstream arena.**

Methods: **Primary data were obtained from records of research conducted internally by tobacco companies and affiliated researchers, and included manuscript drafts, presentations, protocols, and instruments relating to internal clinical trials of human tobacco use and exposure.**

Results: **Tobacco industry clinical research has focused on reduced exposure products, most notably Premier, Accord, and Eclipse. The most widely used strategy observed is switching studies, and details of study designs and protocols favored by the industry are described. Key measures include biomarkers of exposure (e.g., cotinine, CO, and specific carcinogens) and acute health effects such as physical health and fitness.**

Conclusions: **Tobacco industry clinical research has used relatively standard switching study methods, but with a broad set of measures. Clinical switching studies have been conducted by the industry primarily to support existing claims or to develop new claims. Knowledge of prior industry activity can guide and inform future public health research efforts. Although industry clinical trial methods are comparable with current mainstream methods, limited information about the validity of outcome measures used limits their viability for immediate adoption in mainstream science.** (Cancer Epidemiol Biomarkers Prev 2009;18(12):3196–208)

Introduction

Tobacco products and nicotine delivery devices known as potential reduced exposure products (PREP) have been introduced by the tobacco industry over the past two decades, with the purported aim of lowering human exposure to tobacco toxicants and thus potentially reduce health risks associated with tobacco use. Comprehensive assessment of PREPs requires investigation at multiple levels, yet few assessment strategies are applied systematically to these new tobacco products. Initial strategies for assessment of the potential for a product to reduce harm depend on demonstration of reduced individual exposure arising from the use of that product and also lowered individual risk. Demonstration of reduced harm at a broader population level requires epidemiologic research, which is usually not feasible in the short term. Therefore, clinical research, which includes measurement of exposure and health effects (i.e., early indicators of disease or injury), is a valuable preliminary step used to determine a product's potential for reducing individual risk.

Recent strategies to assess the capacity for PREPs to reduce exposure have recommended the employment of clinical research methods (1, 2). The primary aim of such research is to establish the relationship between PREP use and exposure reduction. However, factors other than product design may affect the capacity of PREPs to reduce exposure. Clinical assessment strategies allow measurement of phenomena that may themselves influence exposure and thus individual risk, including patterns of use (such as changes in quantity, frequency of use, and combined use of PREP and conventional products), puffing style (topography), subjective responses (such as sensory perceptions of flavor and nicotine dosing effects), and risk perceptions. Other factors may include individual characteristics of the tobacco user (e.g., gender, race/ethnicity, sensory preferences, and metabolic and genetic factors), tobacco use history and current status (type, duration and amount of use, degree of

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dependence), and intentions regarding future use or quitting. Issues in clinical trial design and choice of measures of exposure or health effects must be addressed and resolved satisfactorily to develop standards on the harm reduction potential for a PREP.

In general, clinical trial methods for PREP assessment conducted by independent scientific investigators conform to methodologies used in Food and Drug Administration–defined phase I-IV clinical trials among human subjects (2). The fundamental feature of clinical trials that allows PREP assessment involves forced switching to a new product under investigation. The so-called switching study designs are randomized clinical evaluations where subjects are required to switch from their currently used product to a new reference product, a test product, or stop smoking; a control group that continues to use an original reference product is usually included. Switching studies may accommodate designs that allow shorter- or longer-term exposure, *ad libitum* use versus controlled use, forced switching compared with optional (natural) switching, or combinations of these parameters. Another key consideration is the choice of measures to be used. Biomarkers of exposure are regularly used, including cotinine, CO, and urinary or plasma biomarkers for carcinogen exposure, and such measures have not yet been validated. A full complement of measures should also include tobacco use behavior, such as smoking topography and consumption. Finally, subjective measures that relate to consumer acceptability are essential. These include subjective measures of product effect (urge and withdrawal relief, perceived nicotine effect), risk perceptions, abuse liability, sensory effects (e.g., product taste, aftertaste, bite, kick), social image, and future intentions to use.

A growing body of research has used switching protocols to examine tobacco users' short-term responses to PREPs compared with a conventional product.[6] Another major realm of investigating clinical research methods on PREPs involves work conducted internally by the tobacco industry and made public through litigation. Increasing investment and commitment to PREP development through the 1990s and into the 2000s (3) has prompted the tobacco industry to develop internal methods for assessing individual exposure and harm. Hence, an understanding of industry methods to assess PREPs is imperative to fully inform public health researchers about PREP evaluation strategies. Industry clinical research has the advantage of being tailored to investigate products with highly specific design and use characteristics (4). This industry research may provide a resource for informing the independent scientific community on clinical methods for assessing reducing exposure products. The features and intended use of a PREP should have relevance for decisions about clinical trial methods and measures.

This article examines the internal tobacco industry methods and measures used in developing PREPs.[7] Because a potential wealth of information is available among unpublished internal tobacco industry that has not previously been explored, the present review focuses on analysis of internal tobacco industry documents. We seek to review internal industry documents to determine what methods and measures have been used by the industry and how these compare with independent approaches. The findings will be used to identify potentially fruitful methods not currently used in the mainstream arena and make recommendations to enhance capacity for PREP and new product assessment.

Materials and Methods

Internal tobacco industry documents were identified using databases at Tobacco Documents Online,[8] the Legacy Tobacco Documents Library,[9] and the British American Tobacco Documents Archive.[10] A snowball sampling design was used for text-based and index searches, with an initial set of keywords and phrases (i.e., clinical trial, safer cigarette, switching study, human exposure, reduced exposure), which resulted in the development of further search terms.

Relevant documents included published articles, manuscript drafts, presentations, protocols, and instruments for internal clinical trials of human tobacco use and exposure conducted by tobacco companies and affiliated researchers. Of the ~8,000,000 documents available in the archives, keyword searches produced ~4,400 documents. After eliminating duplicate, redundant, or irrelevant documents, the authors reviewed ~900 documents to identify appropriately detailed descriptions of clinical trials of PREPs. The analysis focused on documents that contained information regarding the tobacco industry's measurement of exposure to harmful constituents and associated health effects among prototypes of products designed with claims of being potentially less harmful than conventional cigarettes. A total of 36 documents are cited in this article, which referenced specific clinical trials or contain supporting information, dating from 1988 to 2006. Some nonindustry research, in the form of peer-reviewed publications, was consulted and referenced in this article for the purpose of contextualizing industry approaches within broader scientific ideas or issues.

Industry document research presents unique challenges, and results should be interpreted within the context of known limitations with respect to availability of documents (5, 6). Industry research is conducted for commercial purposes and is not peer reviewed and cannot be considered conclusive. Further, the terminology, practices,

[6] A summary of studies undertaken and published within the independent scientific community is presented by Hatsukami et al. Clinical trials methods for evaluation of potential reduced exposure products (48).

[7] A note on terminology used in this article. *Biomarker of exposure:* A tobacco constituent or metabolite that is detectable in a biological fluid or tissue; sometimes considered a measure of internal dose. *Biomarker of effect:* Biomarkers of health effects include cellular or physiologic measures that can potentially be used as intermediate indicators of disease and disease risk. The Institute of Medicine uses the term biomarkers of potential harm (also biomarker of disease), but the term "biomarkers of effect" is used by the tobacco industry and is differentiated from indicators of acute health effects. They include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes "preclinical changes." *Acute health effects or health indicators:* Effects on human health as a result of short-term exposure. Examples of industry studies examining acute health outcomes after PREP use include respiratory symptoms and cardiopulmonary exercise capacity. At this stage, studies of chronic health effects (i.e., cancer) from use of PREPs have not been found in internal tobacco industry documents.

[8] http://www.tobaccodocuments.org

[9] http://legacy.library.ucsf.edu

[10] http://bat.library.ucsf.edu

and methods vary from company to company and over time, and it is important to consider the body of evidence before drawing conclusions on industry activities and their implications for public health.

Results

Use of Switching Studies in PREP Evaluation. All of the 12 detailed clinical studies of PREPs identified in the industry documents used a switching design. An additional study that did not involve a switching design and was not specific to PREPs, Philip Morris' Total Exposure Study, was included in this review to catalogue the extensive use of biomarker measures in the study (7). As opposed to a clinical trial of PREPs, the Total Exposure Study was a large (N = ~5,000) observational, cross-sectional study of exposure and effect measures in adult smokers in the United States, according to the Federal Trade Commission (FTC) tar delivery of their usual brand (7). Internal industry documents suggested that the majority of industry clinical trials of products designed to reduce exposure focused on heated or unburned tobacco products (i.e., Premier, Accord, or Eclipse). Of the 12 industry switching studies reviewed for this article, all evaluated heated or unburned tobacco products (8-19). One study evaluated snus in combination with another PREP and a conventional cigarette (20). Six of the reviewed studies were sponsored by Philip Morris, and seven were supported by RJ Reynolds. The clinical trials were conducted and/or reported between 1988 and 2006, with sample sizes ranging from 18 to 5,000, with a median of 80 subjects (Table 1).

No internal clinical trials of conventional cigarettes (i.e., "lights" compared with full flavor) were found in this search of the documents. Document searching conducted specifically to locate clinical trials among human subjects that evaluate health exposure and effects of "light" or low-tar cigarettes (i.e., using the keywords "clinical trials" and "low-tar" to find documents dated before 1985) revealed no such studies. Although these studies were conducted in the scientific literature, industry assessments of "lights" seem to be limited to toxicology testing, *in vitro* and animal studies, human topography studies, and sensory assessments, all of which are reviewed in companion articles (21). Before the advent of the concept of reduced harm products, the term "switching study" was used internally to refer to the tracking and evaluation of brand switching among consumers in a market environment (22-24).

Independent researchers have traditionally used clinical switching designs to evaluate human smoking behavior and exposure outcomes among smokers of "light" and "ultralight" products (22). Beginning in 2000, tobacco companies began to adopt this approach as they sought to provide evidence to support claims that newly developed products yielded lower exposure among adult smokers (23). Major cigarette manufacturers have previously conducted "claims substantiation testing" for a variety of products that purported to offer consumer benefits, such as reduced sidestream (24-26), being fire-safe (27), or reduced odors or staining (28). The goal of generating empirical support for tobacco product design characteristics deemed to be commercially important was thus used with PREPs, and switching study designs became a logical choice for assessment of changes in exposure as well as consumer acceptability. For example, Philip Morris determined that a specific switching design, outlined below, can be used for rapid product screening of reduced exposure products. The sample size (20 subjects in a single arm) was noted by industry researchers to be insufficient to provide support of claims of product safety, although reasons are not specified and the possibility of more robust sample sizes are not explored (29).

Philip Morris has conducted studies of its electrically heated product (Accord) using both ambulatory and inpatient study protocols (usually involving 10 days inclusive of a 2-day acclimation period). RJ Reynolds has also conducted studies of products designed to heat, rather than burn tobacco—Eclipse and Premier—using variations on the general approach adopted by Philip Morris.

Switching Study Designs. The majority of switching studies randomize subjects into study categories ranging in number from 2 to 5, which include experimental (PREP) and control (conventional) products. Due to the noticeable differences between the products, the studies are open label. In confined studies, subjects were randomized into experimental conditions after baseline measurements and acclimation period occur (9). Stratification by gender (13, 30), number of cigarettes per day (i.e., 5-10, 11-20, 21-30; refs. 9, 13), tar and nicotine delivery of usual brand (i.e., <6 mg FTC "tar," 6-13 mg FTC "tar," >13 mg FTC "tar"; refs. 20, 31), and study site has been used (20).

Whereas ambulatory studies universally have allowed *ad libitum* smoking (10, 18, 32), the number of cigarettes smoked per day is generally controlled in inpatient studies (the maximum number of cigarettes in some studies was 30 per day, whereas another study limited subjects to between 10 and 25 cigarettes per day; refs. 9, 30, 33). In inpatient studies, smoking periods are predetermined; subjects may be offered cigarettes but not forced to smoke during evenly distributed times over the course of each day (i.e., every 32 minutes between 7 a.m. and 11 p.m.; refs. 9, 12, 13). Designated nonsmoking times may also be outlined (i.e., from 11 p.m. to 7 a.m.). Subjects had daily allotments of cigarettes established before the study, based on their individual smoking patterns, and were offered opportunities to smoke at specific, regular time intervals to keep the number of cigarettes per day constant over the course of the study. Controlled smoking times ensured that increasing daily cigarette consumption was not a possible route of compensation for the subjects. Although inpatient studies offer greater control over smoking times and number of cigarettes per day, the main limitation identified by industry researchers is the effect the laboratory environment has on determinants of human smoking behavior (i.e., anxiety).

Subject Recruitment and Inclusion Criteria. Documents showed that subjects used in industry research are adults (age 18+ years), and participants over age 65 years are excluded. Studies may focus on specific age groups (i.e., age 30-65 years; ref. 22). Current smokers are defined as individuals who have smoked conventional cigarettes regularly (e.g., 5-25 cigarettes per day) for at least the past 12 months (9, 10, 13). One study required subjects with the same usual brand during the prior 6 months (11).

The studies reviewed suggested that only healthy subjects are included; "healthy" subjects may be defined as

Table 1. Summary of internal industry clinical trials

Authors/ company	Year	Product (s) tested	Outcomes of interest	Study design	Age	Inclusion/exclusion criteria	Stratification
Philip Morris (9)	2001	•Accord •Oasis •Marlboro Lights •Marlboro Ultra Lights •Nonsmoking	Biomarkers of exposure: •COHb •CO •Nicotine and metabolites •NNAL and NNAL-glucuronide •NNK metabolites •CO •Mutagenicity Ames test Biomarkers of effect: •Blood pressure •Pulse rate •Body weight •Hemoglobin •Leukocytes •Platelet factor IV •Von Willebrand factor •Fibrinogen •C-reactive protein •Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol •Hematology •Factor VII •Leukotriene B_4 •Creatine •11-Dehydro-thromboxane B_2 •8-Epi-prostaglandin $F_{2\alpha}$ •Myeloperoxidase •Interleukin-8 •Elstasc/α_1-antitrypsin complex	•*N* = 110 •Duration: 8 d •Controlled smoking five-arm randomized switching design	Adult	•Smoke 5-25 Marlboro Lights cigarettes per day	•Gender •Number of cigarettes per day (11, 11-20, 21 cigarettes/d)
Philip Morris (17)	2001	•Oasis (3 mg FTC tar) •Marlboro Lights (6 mg) •Parliament Extra Light (3 mg) •PM One (1 mg) •Cessation	Biomarkers of exposure: •COHb •Nicotine metabolites •NNK metabolites Biomarkers of effect: •Urinary mutagenicity •Induced sputum inflammatory substance Behavioral and subjective: Smoking diaries	•*N* = 100 •Duration: 10 d •Confined ad lib within-subject pre-post switching design	Not available	•Usual brand is Marlboro Lights	•Not available
Philip Morris (proposed; ref. 17)	2001	•Oasis (3 mg FTC tar) •Usual brand (6, 3, and 1 mg tar) control group	Biomarkers of exposure: •COHb •Nicotine metabolites •NNK metabolites Biomarkers of effect: •Urinary mutagenicity •Induced sputum inflammatory substance Behavioral and subjective: Smoking diaries	•*N* = 100-200 •Duration: 6 mo •Ad lib switching study	Not available	•Not available	•Not available

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Table 1. Summary of internal industry clinical trials (Cont'd)

Authors/ company	Year	Product (s) tested	Outcomes of interest	Study design	Age	Inclusion/exclusion criteria	Stratification
Roethig et al., Philip Morris (8)	2002	•Conventional cigarettes (FTC tar: 11 and 3 mg; nicotine: 0.8 and 0.3 mg) •Electrically heated cigarettes (FTC tar: 3 and 2 mg; nicotine: 0.3 and 0.2 mg) •Nonsmoking	Biomarkers of exposure: •COHb	*N* = 110 •Duration: 10 d •Controlled smoking 5-arm randomized switching design	Adult	•Male and female •Healthy •Smoke 5-25 cigarettes/d	•Gender •Number of cigarettes smoked per day
Philip Morris (13)	2002	•Accord •Marlboro Lights	Biomarkers of exposure •COHb •Venous bicarbonate •Nicotine •Cotinine Acute health effects: Cardiopulmonary exercise testing: •Breathing frequency •Oxygen uptake •Minute ventilation	•*N* = 18 •Duration: three 3-d periods •Confined randomized within-subject three-condition switching design	40-70	•Males •Smoke ≥20 cigarettes/d •Smokers for at least 10 y •Peak on enrollment and screening cardiopulmonary exercise tests must be within 10% of each other •Do not regularly participate in competitive or organized recreational physical activities •Body mass index must be <40 kg/m^2 •No history of coronary artery, cerebrovascular, or pulmonary disease; other cardiac disease; cardiac dysrhythmia; conduction disturbance; acute pericarditis; myocarditis; endocarditis; lower extremity peripheral vascular disease; aortic aneurysm •No malignancies within 5 y before screening except basal or squamous cell carcinoma •No clinically significant gastrointestinal, renal, hepatobiliary, hematopoietic, neurologic, or rheumatologic disorder or chronic infections disease •No clinically significant endocrine disorder except diet-controlled diabetes mellitus type II and hypothyroidism controlled with stable dose for at least 3 mo before enrollment	•Not available

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Table 1. Summary of internal industry clinical trials (Cont'd)

Authors/ company	Year	Product (s) tested	Outcomes of interest	Study design	Age	Inclusion/exclusion criteria	Stratification
			•CO production •Gas exchange ratio •Heart rate •Blood pressure 12-Lead electrocardiogram			•No acute illness, significant trauma, or major surgery within 6 mo of enrollment •No physical handicap or condition that would limit lower body physical exercise •No unstable psychiatric disorder or inability to comply with testing procedures •No history within past 5 y or current use of illicit drugs •No history within the past 5 y of excess alcohol use or current use of more than 2 units/d or 14 units/wk •No use of prohibited medications (included in the Appendix of cited document)	
Philip Morris (Total Exposure Study; refs. 7, 49)	2005	•Usual brand (<3.0 mg FTC tar, 3.0-6.9 mg, 7.0-12.9 mg, >12.9 mg)	Biomarkers of exposure: •Acetonitrile (exhalate and blood) •CO (exhalate) •COHb (blood) •Hb adducts of 3- and 4-aminobiphenyl (blood) •Nicotine (urine) •Nicotine metabolites (urine) •NNAL and NNAL-glucuronide (urine) •Calcium (blood) Biomarkers of effect: •HDL and LDL cholesterol (atherosclerosis) •Triclycerides (atherosclerosis) •Fibrinogen (cardiovascular disease) •hs C-reactive protein (tissue injury) •Total billrubin (depletion of antioxidant capacity) •Von Willebrand factor (endothelial cell damage)	•*N* = 5,000 (four groups of 1,000 smokers by FTC tar yield, 1,000 nonsmoking controls) •Observational, cross-sectional, multicenter study with two assessment visits	Adult	•Not available	•Age •Gender •Body mass index •Geographic region •Ethnic and racial distribution •Socioeconomic Status (income and education)

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Table 1. Summary of internal industry clinical trials (Cont'd)

Authors/ company	Year	Product (s) tested	Outcomes of interest	Study design	Age	Inclusion/exclusion criteria	Stratification
			•Microalbumin (endothelial cell damage) •11-Dehydrothromboxane-B_2 (platelet activation) 8-Epi-prostaglandin-$F_2\alpha$				
RJ Reynolds (pp. 498-504; ref. 19)	1988	•Premier •Reference cigarette (unspecified)	Biomarkers of exposure: •Nicotine (urine) •Cotinine (urine) Biomarkers of effect: •Urine mutagenicity Behavioral and subjective: •Puff profiles Food diary	•N = 72 (31 smokers, 41 nonsmoker controls) •Duration: 42 d •Ad lib within-subject double crossover design •Controlled diet •Monitored consumption of prescription and nonprescription therapeutic drugs •Minimal exposure to chemicals, environmental smoke, and car exhaust	27-50	•Not available	•Gender •Age
RJ Reynolds (18)	1996	•Premier	Behavioral and subjective: •Duration: 2-3 wk •Sensory attribute ratings	•N = 23 or N = 24 •Ad lib within-subject pre-post switching design	Not available	•Usual brand is Premier or conventional cigarette (no specified brand or tar level) for at least 1 y	
Stiles et al., RJ Reynolds (10)	1997	•Eclipse Regular •Eclipse Mild •Conventional cigarette (usual brand)	Biomarkers of exposure: •Serum nicotine •CO •COHb Behavioral and subjective: •Puffing profiles Sensory attribute ratings	•N = 47 (23 Eclipse Regular, 24 Eclipse Mild) •Ad lib within-subject pre-post switching design •Duration: 2 wk (Eclipse Mild) or 3 wk (Eclipse Regular)	31-54	•Smoke ≥20 full flavor or low-tar cigarettes per day •Good physical health	
RJ Reynolds (34)	1999	•Eclipse	Biomarkers of exposure: •Cotinine (urine) •COHb Biomarkers of effect: •Platelet count Acute health effects: •Lung functioning •Airway inflammation •Respiratory symptoms	•N = 80 •Duration: 48 wk •Ad lib within-subject pre-post switching design	19+	•Smoke ≥15 cigarettes/d •Meet ATS criteria for chronic bronchitis	

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Table 1. Summary of internal industry clinical trials (Cont'd)

Authors/ company	Year	Product (s) tested	Outcomes of interest	Study design	Age	Inclusion/exclusion criteria	Stratification
RJ Reynolds (15)	1997	•Eclipse	Biomarkers of exposure: •Nicotine (urine) •Cotinine (saliva) •Nicotine metabolites •Urine mutagenicity Behavioral and subjective: •Puff profiles	•*N* = 36 (24 smokers, 12 nonsmokers) •Duration: 4 wk •Ad lib within-subject pre-post switching design	26-59	•Subjects' workplace do not have smoking bans	
Reynolds (11, 50)	2004	•Eclipse •New Eclipse prototype (3% urea added)	Biomarkers of exposure: •COHb •Nicotine (blood)	•*N* = 36 •Duration: 28 d •Ad lib within-subject double crossover design	21-55	•Smoke full-flavor, low-tar, or ultra-low-tar cigarettes •Smoke usual brand for at least 6 mo •Smoke ≥15 cigarettes/d •Non-RJR employees •No history of heart disease, lung disease, diabetes, liver disease, kidney disease, drug abuse, neurologic disorders, or psychiatric illness	
RJ Reynolds (20)	2006	•Eclipse •Snus •Low-tar, low-nicotine conventional cigarette	Acute health effects: •COPD-related health status measures	•*N* = 2,700 •Duration: 24 wk •Ad lib three-arm randomized switching design	35-55	•Male and female •Smoke >15 cigarettes/d •Smoked for >10 y •Free of clinically significant health problems as assessed by the study PI •Negative pregnancy test at baseline and 12 and 24 wk among female subjects •Subjects over 55 y were excluded due to risk of undiagnosed atherosclerotic cardiovascular disease	•Regular brand (full-flavor, low-tar, ultra-low-tar, menthol)

free of prespecified diseases, which include such chronic conditions as cancer, cardiovascular disease, diabetes, respiratory disease, and HIV/AIDS. Exceptions to these criteria include studies where outcomes have been examined specifically in subjects with smoking-related health conditions such as chronic bronchitis (12, 34). Additionally, subjects cannot be pregnant (13, 17). Studies evaluating health outcomes among switchers may be limited to subjects at risk for smoking-related disease (i.e., age 40-70 years old; ref. 13).

Studies may include a nonsmoker control group (14, 15, 17). According to published research by industry scientists, the nonsmoking group may have a higher attrition rate, and therefore more subjects are recruited for this group than other conditions (35).

Duration of Studies. Subjects in confinement studies are generally switched to the test product for 10 days; this duration includes a standard 2-day acclimation period (9, 13, 30, 33), whereas RJ Reynolds' 1988 evaluation of Premier required a 5-day acclimation period for its 42-day study (19). Studies range in duration from 8 days (9) to 42 days (19). An acclimation period is used to determine the number of cigarettes subjects were allowed to smoke per day; the maximum number smoked per day during the acclimation period determines the maximum amount of the test product subjects smoked per day during the trial (35). Diet is controlled for confined studies to limit the effects of grilled or fried meat and other heavily pyrolyzed food on urine mutagenicity (19).

Sample Size. RJ Reynolds conducted a large-scale switching study on health-related quality of life (*N* = 2,700, with 900 subjects enrolled in each condition; ref. 35). For the most part, industry studies of exposure have been much smaller, typically having 20 subjects per study arm (9, 11, 17, 30, 31, 33). Sample sizes for each condition in switching studies conducted by other researchers range from 3 (13) to 36 (11).

Tobacco companies have argued that detecting differences in biomarkers between study groups may require large sample sizes that would "not be obtainable in a

premarket situation." (37). According to a Philip Morris report to the Institute of Medicine (2000), "factors that enter into play when an appropriate sample size is being determined include the magnitude of the difference in biomarker level and variations in those differences, the parameter of interest, and the effect size, power and level of significance…. Recent evaluations based on the measurement of nicotine and five of its metabolites in urine (38, 39) indicated that a sample size of 4,500 to 5,000 would be needed to determine statistically significant differences" (37). Industry documents reveal the use of biomarkers on smaller, premarket samples in studies conducted by the industry as well as industry research on the magnitude of differences between biomarkers.

Measurement of Outcomes Specific to PREPs. The major outcome variables measured in industry clinical trials are cancer and noncancer biomarkers of exposure, as well as short-term physiologic responses. Subjective measures and smoking behavior records are regarded as important to control for factors that may affect exposure biomarkers and physiologic tests. Such measures have included consumer acceptance and smoking topography.

Biomarkers of Exposure and Effect. Industry switching studies of PREPs designed with heated or unburned tobacco sought to show reductions in exposure as well as early indicators of reductions in adverse health outcomes. Phillip Morris outlined its criteria for selection of biomarkers for mainstream smoke exposure in 2003, which it based on National Research Council guidelines for validating exposure to secondhand smoke as described by Benowitz (40, 41). Philip Morris' selection of biomarkers were based on whether they were unique to tobacco smoke, they were representative of particulate and/or gas phase tobacco smoke, they were representative of potentially health-relevant tobacco smoke constituents, the constituent metabolism was well understood, concentration was reflective of uptake of cigarette smoke constituents, analytic methods were available, a minimally invasive technique was used for obtaining samples, and biomarker concentration increased as smoke intake increases (30). Common biomarkers of exposure included nicotine and its metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) metabolites, carbon monoxide, and mutagenic substances in urine (9). In 2004, Philip Morris International outlined its attempts to select and validate relevant biomarkers used in PREP clinical studies, exploring the sensitivity and specificity of markers for measuring exposure to a variety of smoke constituents in PREP prototypes compared with reference products (33).

Although most biomarkers used by the industry are used to measure exposure, measures of health effects have also been considered although their validity remains undetermined. Industry research provides some indication that subject characteristics may influence measures of health effects and therefore are important to consider in analysis; for example, a 1995 study indicated that only the male participants showed no difference in hematocrit levels between study conditions (31). As recently as 2006, the industry noted that "the availability of … a biomarker that would predict health benefits associated with use of a PREP would be of tremendous utility, particularly one that could be readily applied in large multicenter clinical trials. Unfortunately, no biomarker that would meet this goal is currently available and validated. Nevertheless, a number of candidate biomarkers have been suggested, and several have at least been partially validated as measures of exposure and/or biological effect" (20). Biomarkers of exposure and health effects used by the tobacco industry in clinical trials are summarized in Table 2.

Acute Health Effects. In a 2008 presentation to nonindustry scientists, British American Tobacco (BAT) researchers recommended a battery of measures for assessing early clinical outcomes in switching studies (42). These included self-reported smoking (number of cigarettes, candidate PREPs per day, and time of smoking); smoking topography (puff number, volume, duration, and interval); physiologic response (heartbeat rate, blood pressure, and forced expiratory volume in 1 second: FEV_1); filter analysis to provide yield in use; general biomarkers of exposure (nicotine, nicotine metabolites, and exhaled carbon monoxide [CO] or carboxyhemoglobin [COHb] levels); and specific biomarkers of exposure (i.e., for toxicants expected to be reduced by the candidate PREP based on smoke chemistry). Recommended longer-term measures included biomarkers of exposure and health effects, physiologic parameters, respiratory symptoms questionnaires, and short-term epidemiologic endpoint evaluations (40).

RJ Reynolds sponsored a study of changes in physical symptoms among subjects with subclinical respiratory tract inflammation upon switching to Eclipse (34). Lower respiratory tract inflammation was assessed bronchoscopically, quantified through a visual scoring system outlined in Thomson et al. (43). Inspection of the airways was done and visually apparent inflammation was scored. Bronchoalveolar lavage was taken of the opposite lung.

Health-Related Quality of Life. A 24-week switching study of Eclipse, snus, and conventional cigarettes focused on chronic obstructive pulmonary disease (COPD)-related health status and selected biomarkers (20, 36).

The primary outcome measure was the St. George's Respiratory Questionnaire (SGRQ), a disease-specific, validated instrument designed to measure impact on overall health, daily life, and perceived well-being (44). Secondary assessments were made with instruments that assess cough, sputum, and symptoms of COPD and that have proved sensitive to smoking behavior [Smoking Cessation Quality of Life Questionnaire (SCQoL), Leicester Cough Questionnaire (LCQ), American Thoracic Society (ATS) respiratory disease questionnaire, and SF-36].

All measures were collected at baseline. These measures were as follows: ATS questionnaire, Fagerstrom Scale of Nicotine Dependence, Stage of Change assessment, SGRQ, SCQoL, LCQ, measures of oral health, pulmonary function tests, blood chemistry and complete blood count, exhaled breath condensate, serum for biomarkers and COHb, 24-hour urine, health history, physical examination, electrocardiogram, exhaled CO, interval smoking history, and a daily diary of usage. All measures, except for electrocardiogram and the Fagerstrom scale, were administered again at visit 9. SGRQ and LCQ were administered at visits 4, 5, 7, 9, and 15. Exhaled CO was collected every time except on visits 6, 8, 10, 12, and 14.

Exercise Capacity. In 2002, Philip Morris researchers sought to compare measures of exercise capacity in a switching design among human subjects using a conventional

Table 2. Industry measures and instruments to assess exposure and health indicators in human subjects

Measures	Biomarkers or outcomes of interest	Examples of products assessed
Physiologic measures		
Heart rate Skin temperature; blood pressure; Body weight (9)	Risk of cardiovascular, renal, and other diseases	Accord, Eclipse, denicotinized cigarette, conventional cigarette
Blood (8-11, 18, 30, 31, 33)	Biomarkers of exposure •Nicotine metabolites •Carboxyhemoglobin •Nitrosamine adducts (NNK) •PAH adducts •Aromatic/heterocyclic amine adducts •Aldehyde adducts •Volatile hydrocarbon adducts and metabolites •Organic compound adducts (e.g., ethylene oxide) Biomarkers of effect •White blood cell count •Cell differential •Platelet count •% Lymphocytes •% Neutrophils •% Monocytes •C-reactive protein (blood serum) •Fibrinogen (blood plasma)	Accord, Eclipse, denicotinized cigarette, conventional cigarette
Exhaled air (33)	Biomarkers of exposure •Carbon monoxide Biomarkers of effect •H_2O_2 in exhaled breath condensate •Airway nitric oxide (measure of airway inflammation)	Accord, Eclipse, denicotinized cigarette, conventional cigarette
Urine (33, 34)	Biomarkers of exposure •Nicotine metabolites •Nitrosamine metabolites (NNK) •PAH metabolites •Urine mutagenicity Biomarkers of effect •DNA adducts	Accord, Eclipse, denicotinized cigarette, conventional cigarette
Cardiopulmonary exercise testing (13)	Exercise capacity/perceived exertion	Accord vs Light conventional cigarette
Bronchoscopic inspection (31)	Lower respiratory tract inflammation	Eclipse use among regular smokers
Smoking behavior		
Smoking behavior questionnaire (51)	Smoking activities (*a*) 2 d before and (*b*) on the same day of biomarker collection	Accord vs Ultra Light conventional cigarette
Subjective measures		
Product assessment questionnaire (51)	Subject's rating of cigarette attributes	Accord vs Ultra Light conventional cigarette
Fagerstrom questionnaire (41)	Nicotine dependence	Accord vs Ultra Light conventional cigarette; Accord vs Light conventional cigarette
Diet, consumption, and physical activity questionnaire (50)	Level of physical fitness, exposure from food	Accord, Eclipse, denicotinized cigarette, conventional cigarette

cigarette, an electrically heated PREP, and a nonsmoking condition (13). Cardiopulmonary exercise testing was conducted at the end of each 3-day exposure period using a cycle ergometer, treadmill ramp with a continuously increasing work rate, and expired air analysis. Gas exchange and hemodynamic parameters were measured at rest, during 3 minutes of a low level of exercise (unloaded pedaling at 60 rpm), during a continuously increasing work rate, at maximum exercise, and during recovery. These measures include breathing frequency, minute ventilation, oxygen uptake, carbon dioxide production, gas exchange ratio, heart rate, blood pressure, and 12-lead electrocardiogram.

Internal Tobacco Industry Research Standards. Tobacco company documents provide evidence that proposals are subject to review by internal human subjects committees (9, 11, 45). However, certain practices used in industry clinical trials may not pass similar review in academic or independent scientific settings. Nonsmoking subjects, for example, have been allocated to experimental conditions that require them to use a conventional or novel tobacco product (9). As has been documented elsewhere, it was common practice for tobacco companies to recruit employees for sensory testing for product development (46, 47). These practices continued with industry clinical trials of PREPS (10, 18). Documents occasionally referred to subjects as "volunteers" without mention of compensation or incentive payments (29).

Industry research revealed that subjects using Premier exhibited higher levels of COHb compared with control groups, which was attributed to subjects' puffing while the product was generating very little smoke yield, although the carbon fuel remained lit (a feature that

indicates that the product is being used). Industry personnel instructed users of the test product who were concerned about elevated CO to adjust their smoking topography by ceasing to use the product after they found it difficult to generate smoke. It is unclear from the documents whether such instructions were provided to study participants, but reveals that such industry knowledge of product design allows for the possibility of creating study conditions that can influence the health-related outcomes generated (23).

Discussion

Internal tobacco industry documents show that clinical trials have been performed to provide support for claims of reduced exposure and health risk. Twelve previously unpublished clinical trials conducted by Philip Morris and RJ Reynolds were reviewed, as well as a large-scale observational study of human exposure to harmful constituents among smokers using conventional cigarettes. These studies were done between 1988 and 2006, and all compared products that electrically heat tobacco to a conventional tobacco-burning cigarette; one study also included a pouched smokeless tobacco product, snus, as a switching condition. Tobacco industry PREP use of switching studies seemed to accelerate in the late 1990s with the advent of Accord (Philip Morris) and Eclipse (Reynolds) products, apparently in response to the Master Settlement Agreement of 1998 and the threat of further litigation and possible Food and Drug Administration regulation of tobacco products. The internal documents provide a valuable insight into product-specific methodology used to defend harm reduction claims from potential regulatory or legal challenges, and such methodology should therefore be accorded high significance by the public health community as tools for PREP assessment.

Before the development and sale of PREPs, tobacco companies manufactured light and ultralight machine yield products, which also were marketed with implicit health-related product claims. However, tobacco industry research, conducted as far back as the 1960s, was aimed primarily at assessing consumer acceptance of low-yield cigarettes. The present findings show that, unlike early research on low-yield products, the tobacco industry has conducted clinical trials with PREPs to generate empirical support for health-related product claims. The evidence suggests that research has been conducted on only a limited range of commercially known PREPs. Hence, it seems that the use of clinical trials to develop a science base for health-related product claims is a relatively new function of the tobacco industry. The earliest example of such work was extensively documented in 1988 by Reynolds in their Premier research monograph (19). Other switching studies have been conducted chiefly by Philip Morris and RJ Reynolds on their respective heated but not burned products, Accord and Eclipse. Less extensive internal documentation indicated that switching studies have been conducted on pouched snus products. No documents were identified that reported internally conducted switching studies with conventional-style PREPs, such as Marlboro UltraSmooth or Quest, or pouched snus products recently developed by cigarette manufacturers, such as Camel Snus or Marlboro Snus.

In general, the research strategies used by industry have been similar to those used in independent research. In using switching designs, the tobacco industry is adhering to a widely used, "gold standard" approach to assessing the effects of product substitution most often used by the pharmaceutical industry. Standard manipulations such as randomization to subgroup and incorporation of controls were also observed. Other industry design manipulations recognized in the independent research arena include stratification of the sample by gender, consumption level and preferred product, and selective inclusion and exclusion criteria based on the study purpose (e.g., no reported adverse health indicators). Although larger studies of sample size more than 1,000 were identified, there was an observed tendency for industry studies to recruit sample sizes of ~20 subjects per group. The rationale for this is not clear and it is presumed that this reflects the minimum needed for statistical power to detect changes in a key outcome measure such as an exposure biomarker. Further scrutiny of a broader range of industry communications may reveal the basis for this apparent standard industry research method.

Perhaps most significantly, outcome measures used in industry clinical PREP evaluations include a focus on two primary outcome domains. Like independent researchers, the tobacco industry has placed a heavy emphasis on biomarkers of exposure to assess the effects of switching from conventional products to PREPs. Important exposure biomarker measures have included cotinine, CO, COHb, and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Evidence also points to the development of biomarkers for mainstream smoke toxins acrolein (3-HPMA), 1,3-butadiene (MHBMA and DHBMA), and polycyclic aromatic hydrocarbons (1-HOP), although results of biomarker research in PREP switching studies were not found. Biomarkers of disease (often referred to in industry communications as biomarkers of effect) that are relatively new or novel to independent research were identified. These included high- and low-density lipoproteins (HDL & LDL) cholesterol, triglycerides, fibrinogen, hs C-reactive protein, and bilirubin. In contrast with much independent research, however, the industry has also used a range of tobacco-related health indicators as outcome measures, ranging from simple acute physical responses to self-reported symptomatology and responses to exercise challenge. Other industry measures that are assessed preswitching and postswitching include consumption, use topography, and subjective measures. These measures tend to be considered as ancillary to the two major outcome measure domains described above and are used to provide a basis for controlling or interpreting changes in primary outcomes.

Because of the limited range of PREP types used in industry clinical trials, evidence for a rule-based approach to selection of outcome measures cannot be determined. It may be reasonable to suppose that an organization responsible for designing a product with claims for harm reduction is also well suited to select the most appropriate measures to show support for those claims. This also implies that assessment methods might be tailored to product design and use characteristics. Evidence for tailored methods was not found, although this may be a function of the limitation of available research on heated or unburned tobacco products. The present review of industry

clinical methodology is notable also for the failure to identify industry use of clinical methods now broadly accepted in mainstream science. For example, switching paradigms that accommodate dual use of a PREP and conventional product, switching to nicotine replacement therapy, or cessation were not observed. As PREP assessment methodology continues to be refined, such methods have become increasingly important to independent investigators. Clinical trial methods need to reflect "real life" use patterns within the context of a research study, including *ad libitum* use of a PREP alone or in combination with conventional products, and employment of rigorous controls such as nicotine replacement therapy or forced switching conditions. Perhaps the narrow objective of demonstrating reduced exposure risk compared with a conventional product in support of product claims has limited the scope of clinical research methods used by the industry.

Industry clinical assessment methods reveal relatively little about choosing specific measures for assessment of a specific product and the resulting range of claims that could be presented. Industry clinical assessment methods tend not to adopt specific measures to evaluate specific PREP products. Instead, the tobacco industry has used relatively standard clinical methodologies, but with perhaps a broader set of measures than are used in the mainstream community. The independent research community has identified the need for biomarkers of health effects for a range of health outcomes to ensure that products do not selectively decrease risk for certain diseases at the expense of other diseases (2). Rather than focusing on outcome measures that reflect specific diseases, industry research typically uses a broad range of measures that provide a basis for detecting changes in exposure beyond immediate claims or likely health benefits. For example, PREPs such as Omni have referred to reduced cancer risk, whereas Eclipse has referred to reduced risk for respiratory illness. Research with Eclipse included exposure measures CO and cotinine, as well as health indicators such as diet, consumption, and physical activity—measures that are not necessarily immediately related to respiratory disease.

These findings suggest that internal tobacco industry research is a useful reference with which the state of the art in assessment methods used by the mainstream research community can be compared. Although industry methodology should not be adopted uncritically by independent researchers, knowledge of industry strategies and tools is a useful guide in determining methods for product assessment. Critical examination of industry methods has the potential to inform us about promising novel methods. The tobacco industry has pioneered strategies to assess variables not previously considered by mainstream scientists, such as participant ratings of product sensory effects (4). In the present review, few new methods were identified; indeed, industry methods tended to reflect those that have been established by independent investigators. This observation suggests that tobacco manufacturers have been influenced by mainstream science practices in their adoption of clinical trial methods. The relatively limited scope of products evaluated clinically by the industry and the lack of information about validation of measures means that specific recommendations for informing future clinical methodology are not possible. Methods that have been identified as well established and widely used in medical and behavioral research arenas may continue to offer the best choices for future clinical research (48).

Finally, scrutiny of industry research and the methods used may assist the public health community to anticipate and respond to new product claims. One important purpose of industry clinical research seems to support existing product claims or to consider new claims. Claims made on the basis of questionable science and claims for which adequate evidence does not exist may be more expediently assessed through initial examination of internal industry research. However, internal industry documents of the sort reviewed here are not systematically organized, are challenging to locate and interpret, and cannot be assumed to be comprehensive or up to date. Further, industry clinical methods may continue to evolve, especially with the advent of newer smokeless products and other novel products. The U.S. Family Smoking Prevention and Tobacco Control Act of 2009 gives the Secretary of Health and Human Services the authority to request a wide range of internal documentation from tobacco manufacturers on their research activities and findings. Making such industry data publicly available would enable the public health community to adequately evaluate implicit or explicit product claims and could help to avoid public misperceptions about the potential for PREPs to reduce risk. Additionally, tobacco manufacturers making any health-related claim should be required to provide empirical evidence in support of that claim, including methods and research data, for review by appropriately qualified independent scientists. Research independent of the tobacco industry is essential to provide an effective and unbiased evaluation of industry claims. Although disclosure and review of internal tobacco industry research is an important step in evaluating manufacturer claims, claims for PREPs, both implied and explicit, must ultimately be evaluated independently, by the broader scientific community, using validated assessment strategies and accepted clinical methodology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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