# DO EFFICACY CLAIMS IN PHARMACEUTICAL SALES VISITS VARY BY APPROVED PRODUCT INFORMATION OR NATIONAL POLICY?

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TITLE: Do Efficacy Claims in Pharmaceutical Sales Visits Vary By Approved Product Information Or National Policy?

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## ABSTRACT

**Introduction:** Pharmaceutical sales visit claims of drug efficacy can influence physician prescribing. Efficacy claims may be susceptible to exaggeration in promotions for drugs approved on the basis of surrogate outcomes. They may also be different in countries with different sales visit regulations.

**Objectives:** To compare the frequency of physician-reported claims of serious morbidity or mortality benefit in promotions for drugs approved on the basis of surrogate outcomes (where claims are unwarranted) with those approved on the basis of serious morbidity or mortality. Additionally, to compare the frequency of unwarranted claims of serious morbidity or mortality benefit by country of promotion.

**Methods:** From 2009 to 2010, primary care physicians in Canada, France, and the United States reported via pre-set questionnaires on claims of serious morbidity or mortality benefit in consecutive cardiovascular drug promotions. Promoted drugs were either 1) approved on the basis of surrogate outcomes, or 2) approved on the basis of serious morbidity or mortality. Using generalized estimating equations, the frequency of reported efficacy claims was compared between the two promotion types. The frequency of unwarranted claims drug benefit was also compared by country.

**Results**: 448 promotions were analyzed. Claims of serious morbidity or mortality benefit were reported in 156/347 (45%) promotions for drugs approved on the basis of surrogate outcomes and 72/101 (71%) promotions for drugs approved on the basis of serious morbidity or mortality, $p<0.001$. Despite stricter sales visit regulations, unwarranted claims of serious morbidity or mortality benefit for drugs approved on the basis of surrogate outcomes were reported most frequently in France (59%) compared to Canada (46%), $p=0.2$ or the United States (26%), $p=0.02$.

**Conclusions:** Across countries, unwarranted claims of drug benefit were frequently reported in promotions for drugs approved on the basis of surrogate outcomes. These claims amount to off-label promotion and contravene national sales visit regulations.

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| | |
|---|---|
| **ASMR** | Amélioration du service médical rendu [Rating of added drug therapeutic value] |
| **CAD** | Coronary artery disease |
| **CEPS** | Comité économique des produits de santé [Health Products Fiscal Committee] |
| **CHF** | Congestive heart failure |
| **EMA** | European Medicines Agency |
| **FDA** | Food and Drug Administration |
| **F&DA** | Canada Federal Food and Drugs Act |
| **FD&CA** | United States Federal Food, Drug and Cosmetic Act |
| **GAO** | United States Government Accountability Office |
| **GEE** | Generalized Estimating Equations |
| **HbA1c** | Glycosylated hemoglobin |
| **HF** | Heart failure |
| **LEEM** | Les entreprises du médicament [French Pharmaceutical Industries] |
| **LDL-C** | Low-density lipoprotein cholesterol |
| **MI** | Myocardial infarction |
| **OR** | Odds ratio |
| **CI** | Confidence interval |
| **PAAB** | Pharmaceutical Advertising Advisory Board |
| **PSR** | Pharmaceutical Sales Representative |
| **Rx&D** | Canada's Research-Based Pharmaceutical Companies |
| **SMR** | Service médical rendu [Rating of drug therapeutic value] |
| **WHO** | World Health Organization |

## GLOSSARY (DESCRIPTION OF TERMS USED IN THIS THESIS)

**Original cohort study:** Prospective cohort study (2009-2010) by Mintzes and colleagues which examined the content of sales visit promotions in Vancouver and Montreal (Canada), Toulouse (France) and Sacramento (United States), as reported by primary care physicians (1). Data for the thesis was obtained from this study.

**Clinical outcome drug:** Drug approved by the relevant drug agency on the basis of serious morbidity or mortality outcomes.

**Pharmaceutical sales representative (PSR):** Employee of a brand-name company who visited the physician's practice to promote one or a more company-specific drugs to physicians in a one-on-one or group setting.

**Pharmaceutical sales visit (or "sales visit"):** Instance where the PSR visited the physician's practice for the purpose of promoting one or more company-specific drugs.

**Promotion:** Instance during a sales visit where the PSR made at least 1 efficacy claim about a brand name drug.

**Promotional materials:** Any variety of communication media, including sales visit aides, journal advertisements and internet advertisements, targeting healthcare professionals to promote one or more company-specific drugs.

**Serious morbidity or mortality outcome:** A fatal or non-fatal serious cardiovascular or cardiovascular disease-related outcome. Specifically: myocardial infarction (MI), stroke, coronary artery disease (CAD), heart failure (HF), congestive heart failure (CHF), chronic stable angina, or renal disease.

**Surrogate outcome:** A biomarker intended to substitute for a clinical endpoint and expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

**Surrogate outcome drug:** Drug approved by the relevant drug agency on the basis of surrogate outcomes.

**Unwarranted efficacy claim:** A claim of drug efficacy on serious morbidity or mortality in a sales visit promotion for a drug that was approved by regulators on the basis of surrogate outcomes.

# 1. INTRODUCTION

## 1.1 Drugs approved on the basis of surrogate outcomes

### 1.1.1 Appraising drug efficacy and safety on the basis of surrogate outcomes

Ideally our understanding of drug efficacy and safety would always be based on randomized controlled trials (RCTs) testing drugs on patient-important clinical outcomes. Clinical outcomes, such as the incidence of stroke, or health-related quality of life, are measures of how a patient feels, functions or survives (2). However, the randomized trials used to gain regulatory approval for drugs frequently use laboratory or physiological measures referred to as surrogate outcomes (3). Surrogate outcomes are biomarkers intended to substitute for a clinical endpoint and expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence (4). Surrogate outcomes may range from physiological variables such as blood pressure, lipid levels, and glycosylated hemoglobin (HbA1c), to subclinical disease measures such as the progression of atherosclerosis on ultrasound examination.

When evaluating drug efficacy, regulatory agencies generally accept the use of certain validated surrogate outcomes as substitutes for patient-important clinical outcomes (5,6). Between 2009 and 2010, surrogate outcomes were used in more than half of all trials submitted to the EMA to obtain drug marketing authorization (7). Of the 448 efficacy trials used by the United States (US) Food and Drug Administration (FDA) to approve novel drugs between 2005 and 2012, nearly half used a surrogate outcome as the primary endpoint (8).

Advantages to evaluating drug efficacy and safety using surrogate outcomes include the fact that smaller sample sizes and shorter trial durations are needed

compared to trials employing clinical outcomes. By extension, trial sponsor costs are reduced, and fewer patients are exposed to experimental interventions. Expedient clinical trials may also translate to quicker market access to new drugs, which may be an important consideration for medical conditions lacking therapeutic options. By first granting approval on the basis of trials employing surrogate outcomes, for instance, patients were able to benefit from efficacious antiretroviral drugs during a period of high need while drug effects on AIDS-related mortality were confirmed in post-market analyses (9,10).

Use of surrogate outcomes is also countered by important drawbacks, however. The surrogate outcome may not adequately predict overall drug effects on patient-important clinical outcomes (11). Correlation between a surrogate and clinical outcomes is an insufficient criterion of validity (12). The surrogate outcome must be in the causal pathway of the disease, and changes in the surrogate outcome must also predict all changes to the clinical outcomes of interest (2).

Demonstrating that a surrogate outcome answers to the above exigencies requires substantial effort (13). If a surrogate outcome lies outside of the causal pathway of the disease, or if it lies in just one of many disease pathways, there are risks of false negative or positive conclusions. Moreover, even if the surrogate outcome lies in the correct pathway, off-target effects of the drug may impact other important clinical outcomes not readily identified in the small scale, short-term trials using surrogate outcomes. The arrhythmia-suppressing drugs encainide and flecainide, thought to reduce the risk of sudden cardiac death, are a textbook example of where an eventual clinical outcome trial (CAST) recast drug efficacy profiles by showing that these drugs in fact tripled the death rate (14).

As one of the leading causes of death worldwide, the risk factors associated with cardiovascular disease have been extensively studied (15). Drugs for the treatment and prevention of cardiovascular disease, including myocardial infarction (MI), angina, and stroke, are generally approved by regulators on the basis of their effects on known risk factors (and surrogate outcomes), including blood pressure, low-density lipoprotein cholesterol (LDL-C) levels, and serum HbA1c (in the case of diabetes patients at risk of cardiovascular disease) (16). Owing to the multi-factorial nature of cardiovascular disease, no single risk factor may fully predict drug effects across various drug classes (17).

Recent developments on the safety of rosiglitazone (Avandia) further illustrate the uncertainty associated with approving drugs on the basis of surrogate outcomes. Rosiglitazone activates gene transcription to enhance insulin sensitivity in type 2 diabetic patients, thereby lowering serum HbA1c levels. At the time of Health Canada's approval of the drug, this HbA1c-lowering effect was presumed to lower the risk of diabetes-related cardiovascular complications. Since 2007, however, several independent (18-21), and regulatory agency-led meta-analyses (22) have indicated that rosiglitazone is associated with risks of MI, heart failure (HF), and cardiovascular-related mortality.

To contend with the limited available evidence on benefits and harms when drugs first come to market, regulators may undertake or request drug sponsors to conduct post-marketing studies to confirm long-term drug efficacy and safety. Results of post-marketing studies however, take years to materialize, and when available, they may still not provide the conclusive evidence needed to support post-market regulatory decision-making. In the case of rosiglitazone, a prospective controlled trial

designed to evaluate cardiovascular outcomes (RECORD) spurred disagreement in the medical community about the real cardiovascular risks presented by the use of rosiglitazone. Concerns about trial design (in particular that the study was open-label with a sample size lower than most trials needed to evaluate cardiovascular outcomes) limited the utility of findings (23). This disagreement also manifested internationally, when in 2010 the EMA decided to withdraw the drug, while both Health Canada and the FDA opted to restrict access but maintain marketing authorization on the basis of the same evidence (24).

More fundamentally, post-marketing studies may remain unaccounted for well after marketing approval. In analyzing the FDA's oversight of drugs approved on the basis of surrogate outcomes, for instance, the US Government Accountability Office (GAO) found that only half of the 179 post-market studies required by the FDA for surrogate outcome-based drugs approved between 1998 and 2008 had been completed in 2009 (25), and since 2008, only 31% of new drugs approved by the FDA had fulfilled post-marketing commitments (26). Deficiencies in the accountability of post-marketing commitments have also been described in Canada, and in European countries (27).

### 1.1.2 Clinical practice and the interpretation of surrogate outcomes

The results of clinical trials using surrogate outcomes only can also be misinterpreted. In a study comparing trials using only surrogate outcomes to those using clinical outcomes, treatment effect estimates were on average 47% larger in binary surrogate outcome-only trials compared to trials employing binary clinical outcomes, even after adjusting for trial sample size (28). Surrogate outcome-only trials also had more than two times the odds of leading to positive conclusions about

treatment (62% or 52/84 trials) than trials using clinical outcomes (37% or 37/101 trials), even after adjustment for trial characteristics such as the publishing journal. These uncertainties help to explain why health technology assessment agencies such as the Canadian Common Drug Review often cite the use of surrogate outcomes in submissions as one of the main barriers to adequately assessing the therapeutic value of a drug (29).

Making decisions about the therapeutic value of a drug evaluated on the basis of surrogate outcomes may be even more difficult for physicians in clinical practice, whose concern is to extrapolate the findings of clinical trials to the unique needs of the patient before them. Physicians prefer to use scientific knowledge when making prescribing decisions (30), and given that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), they should be able to readily identify when surrogate outcomes have been used as primary outcomes in trials. They should also be given enough information to appraise the validity of the surrogate outcomes used.

An analysis of clinical trials published in six major medical journals between 2005 and 2006 (31), however, suggests that access to this information may be unreliable: only 62 of 109 trials examined clearly described the surrogate as a primary outcome and of these 62, 39% failed to discuss the validity of the primary surrogate outcome. More generally, it can be difficult to obtain a complete understanding of drug efficacy and safety profiles when the scientific literature is more likely to consist of papers with statistically significant and positive findings about therapeutic intervention than non-significant or negative conclusions (32,33). News outlets covering clinical trial results may also mislead professional and public audiences on

the true risks and benefits of therapy, via undue emphasis on relative versus absolute risk reduction and benefit more than harm. Media articles supported the continued use of fenofibrate in diabetic patients (34) despite the results of the landmark ACCORD trial providing conclusive evidence that the drug did not lower overall cardiovascular risk in patients with diabetes (35).

In light of these uncertainties, we might expect that physicians would be reluctant to prescribe a drug approved on the basis of surrogate outcomes over another in the same therapeutic area with established effects on clinical outcomes that are important to patients. This does not appear to be the case. An analysis of prescribing rates of lipid-lowering drugs from 2002-2006 showed that the prescribing of ezetimibe (Vytorin), which was approved only on the basis of change in lipid levels rather than improvement in cardiovascular event rates, rose sharply in the US and reduced the market share of statins whose effects on clinical outcomes were well established (36).

A retrospective analysis subsequently examined the prescribing patterns of ezetimibe in the US, using data from a large pharmacy benefit manager, before and after the 2008 appearance of the first large-scale efficacy trial for this drug (ENHANCE) (37). Although ENHANCE showed that the drug did not slow progression to atherosclerosis despite lower LDL-C levels (38), trial evidence did not impact prescribing in predictable ways: ezetimibe monotherapy prescriptions rose, while concomitant therapy with other lipid-lowering agents diminished. A similar US study analyzed the 7-year prescribing patterns of fenofibrate, another lipid-lowering drug with mixed evidence of beneficial effects on clinical outcomes (39). Fenofibrate prescribing increased throughout the study period, at double the rate at which statin prescribing rose during the same time period (40).

There may be various reasons why physicians choose to prescribe drugs approved on the basis of surrogate outcomes even when the evidence may point to more preferable drug and non-drug alternatives. Current guidelines and quality measures in clinical practice, for instance, encourage the attainment numerical goals, such as reduction of LDL levels, that are readily achievable through the prescribing of surrogate outcome-based drugs (41). Pharmaceutical promotion, and the information provided to physicians through this medium, may be another important source of influence over prescribing decisions.

**1.2 Pharmaceutical promotion**

The World Health Organization (WHO) defines pharmaceutical promotion as "...all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs" (42). Depending on the national regulatory framework, promotional activities may include, among other activities, pharmaceutical sales visits, advertisements in print or online academic journals, scientific conferences, direct-to-consumer advertising, and social media.

A substantial portion of the pharmaceutical industry's revenue is allotted to marketing efforts. From an audit of 34 countries (including the US and France), the healthcare market research company Cegedim Strategic Data pegged the world's pharmaceutical promotional spending in 2013 at $85 billion USD (43). According to these estimates, promotional spending in the US accounted for approximately $28.3 billion USD annually or 33% of the world's market share (44), while in France, spending was at $3.61 billion USD (45). Although there are no recent figures of promotional spending in Canada, estimates based on the types and cost of Canadian

promotional activities range from $2.4 to $4.7 billion CAD annually (personal communication, Joel Lexchin, October 27 2014).

Pharmaceutical sales representative (PSR) visits to physicians consistently rank as the largest promotional spending category for companies worldwide (43). Topics of discussion during the sales visit may include the benefits, indications, and risks of one or a few drugs marketed by the company. Free samples of promoted drugs may also be provided. The predominant model of remuneration for PSRs, typically consisting of a base salary topped with incentive-based commissions, also encourages representatives to present messages that will increase the sales of promoted drugs (46).

### 1.2.1. Influence of the pharmaceutical sales visit

Interactions with the pharmaceutical industry have been documented as early as the first year of medical school (47), and medical trainees' reliance on sales representatives for drug information has been found to increase as students progress into residency (48). Physicians may consider themselves to be impervious or only mildly susceptible to promotional influence (49-51). The more frequently physicians receive sales visits, the more likely they are to dismiss the notion of being influenced (52), and while physicians may recognize the biases inherent to the sales visit, they tend to perceive their colleagues as more impressionable than themselves (49).

Nevertheless, the influence of sales visits on physician prescribing is well-documented both in the academic literature (53-55) and in market research (56-58). Requests for drug formulary additions, for instance, appear to be influenced by the sales visit (59,60) as is the decision to start patients on a new prescription drug (61-63).

In a 2010 systematic review, information provided during the sales visit was associated with increased target drug prescribing in 17 of 29 studies, while no studies found an association with decreased prescribing (55). The frequency of sales visits received was also associated with a wider prescribing range (64), less adherence to prescription guidelines (65), and reduced quality of prescribing in simulated case histories where the new drug was first heard about during the sales visit (66).

A more recent study suggests that, as early as medical school, positive attitudes about pharmaceutical promotion may be associated with less evidence-based prescribing decisions. A survey of over 2000 medical students and residents in the US found that a 10% increase in the industry relations index, which measured the degree to which students found pharmaceutical promotion to be acceptable, was associated with a 15% lower odds of making evidence-based prescribing choices in response to common clinical scenarios (67).

In France, a thesis study using data from the national healthcare program found the medication choice of a random sample of 179 physicians to be associated with the frequency of PSR visits (68). Physicians seeing PSRs more frequently prescribed pioglitazone (withdrawn from the French market in 2011 because of safety issues) and gliptins, drugs with less certain efficacy profiles, over more established oral antidiabetics. They were also more likely to choose the costlier angiotensin receptor blockers over angiotensin-converting enzyme inhibitors, despite recommendations by the French National Health Authority that the latter should be the first choice where a renin-angiotensin inhibitor is being considered to treat essential hypertension (69). The evidence suggests that pharmaceutical sales visits can have a negative impact on the quality, frequency, and cost of prescribing. This may

well be due to the information provided during the sales visit.

### 1.2.2. Information provided during the pharmaceutical sales visit

When regulators approve a new drug, they also approve the accompanying product information (referred to in Canada as the “Product Monograph”). The Product Monograph summarizes the scientific evidence submitted to the regulatory agency and provides instructions for the drug’s use, and the condition(s) and patient population(s) for which the drug is approved (the ensemble of which is known as the "indications"). In most countries, regulations governing pharmaceutical sales visits require, at a minimum, that information provided during the visit be consistent with approved product information, and that the information not be false or misleading (70).

The literature suggests, however, that the quality of information provided in sales visits, both through verbal (i.e., conversational) and non-verbal (i.e., article reprints, brochures, and sales visit aids) media is variable and can be inconsistent with regulatory requirements. An analysis of the information contained in 482 materials given during sales visits in the US found a predominance of information on drug benefits over harms in one third of the materials, despite the fact that fair balance of harm and benefit information is required by the FDA (71). Overall, 42% of materials contained a violation of FDA regulations on promotion (for more details see section 1.3.3).

Results from three studies using direct observation methods to analyze orally presented information in Finland, and Australia also found that PSRs mentioned the neutral or positive aspects of drugs, such as generic names and indications, far more frequently than negative ones (72). Across these studies, information on drug side

effects was provided (usually in response to questions) in approximately 25% of the 148 sales visits analyzed.

More recent analyses relying on physician self-reports in several countries reveal a still-prevalent tendency to omit harm information during sales visits. In a 15-year survey ending in 2005, physicians who subscribe to the French medical journal *La Revue Prescrire* anonymously volunteered as observers in a sentinel network monitoring the messages received during their visits with PSRs (73). Consistent results were obtained throughout the study period, with information on contraindications, adverse effects, and drug interactions seldom being provided (mention of any of these items ranged from 8 to 35% in any given year). A prospective observational study in Australia and Malaysia also found a lack of information on harms (defined as contraindications, drug-drug interactions, and adverse effects) in approximately half of all promotions (n=183) (74). In a 2009 and 2010 prospective cohort study of primary care physicians in Canada, France, and the US receiving sales visits for drugs with black box warnings, information about serious adverse effects was mentioned in 7% of 962 such drug promotions (1).

Beyond omissions of negative drug information, sales visits may also contain false or misleading claims about the uses of a drug. When a drug is promoted for unapproved uses the promotion is said to be "off-label". A drug can be promoted off-label in several ways: use of the drug may be expanded to a different condition, to variations of the same condition, to different populations or to unapproved dosing strategies. Although physicians have the legal authority to prescribe a drug off-label, the real harms and benefits of such uses are more uncertain than uses evaluated and approved by a regulatory agency, and physicians may not be aware of what on- or off-

label indications are, even for drugs that they commonly prescribe (75). Off-label promotion is generally illegal in all countries with a functioning system of pharmaceutical regulation, and if detected, its occurrence is usually considered a serious offence by regulators.

Nevertheless, promotion of unapproved uses and misleading efficacy claims are among the most common regulatory violations reported by the US FDA (76). In a study of sales visits for antipsychotic medications, over 90% of physicians practicing in the US Veteran Affairs Department recalled at least one PSR claim that was inconsistent with the FDA-approved package insert of the drug (77). In the 15-year observational study of sales visits in France, unapproved indications were mentioned in nearly one third of sales visits throughout the study period (73).

Lawsuits involving off-label pharmaceutical promotion, while anecdotal, offer a closer look into how off-label promotion may become integrated as part of a company's long-term marketing strategy. Following US litigation involving the promotion of gabapentin (Neurontin), subpoenaed physician-completed market research forms on sales visits revealed that the drug was promoted off-label in 38% of the 115 sales visits analyzed. Nearly half of the 108 physicians surveyed reported an intention to increase their prescribing of the drug regardless of whether an approved on unapproved use was promoted (78).

In 2007, Purdue paid $600 million in a US lawsuit alleging that the company's aggressive marketing campaign promoted the oral analgesic oxycodone (Oxycontin) for a wide range of conditions in the primary care setting, and downplayed the addictive qualities of the drug. From the time of market approval in 1996 until 2000, Purdue more than doubled its PSR sales force and physician call list in the US (79),

and made promotional claims extending the drug's analgesic efficacy in managing cancer-related pain to chronic non-cancer pain such as osteoarthritis (80). The drug's huge commercial success belied the high levels of drug abuse, addiction and deaths reported in areas where the drug was most heavily promoted in Canada and the US (79).

If taken at face value, the omissions and false claims in pharmaceutical sales visits can have negative implications for evidence-based and cost-effective prescribing, and ultimately patient safety. Yet the clinical practice setting may also predispose physicians to relying on information offered by PSRs. According to one observational study, physicians sought answers to only one of every five questions arising in clinical practice (81). Barriers to information retrieval include a lack of time (82), as well as the size and perceived difficulty of filtering evidence in the medical literature (83). As a result of these barriers, more direct sources of information are typically preferred, such as local guidelines, colleagues, and other human sources for updated therapeutic information and advice (81,82,84,85). Physicians generally hold positive opinions about the sales visit (1,53,78), and may view it as a convenient and readily accessible source of information about drugs (86,87).

Given that physicians may come to rely, at least partially, on the drug information provided during the sales visit, regulations are necessary to help control the quality of drug information conveyed to physicians.

### 1.3 Regulation of the pharmaceutical sales visit

The main goal of drug regulation is to ensure public health, and this is achieved by controlling the quality, safety and efficacy of drugs, and the appropriateness and accuracy of product information, including information provided

through promotional activities (88). The 1988 WHO Ethical Criteria for Medicinal Drug Promotion provide an international template of regulatory standards to be adopted by the governments of member countries seeking to control pharmaceutical promotional practices (42). The pharmaceutical sales visit, in particular, can be governed through a combination of legislation, regulation, and guidelines issued by various branches of government, health professional societies, pharmaceutical companies and/or their national or international syndicate organizations, and third party organizations at arms' length from government, such as agencies providing pre-clearance of promotional materials, or health technology assessment organizations. In all but a few countries, however, regulation occurs through voluntary industry codes of conduct (70).

Few studies have compared the characteristics of sales visits across countries with different regulatory frameworks, but in these, differences have been observed in terms of the quality and quantity of information provided by PSRs (1,74). The following sections provide an overview of three distinct approaches to regulating the sales visit: self-regulation in Canada, government regulation with the cooperation from stakeholders including the pharmaceutical industry in France (co-regulation), and direct government regulation in the US.

### 1.3.1. Regulation of the pharmaceutical sales visit in Canada

Under the federal Food and Drugs Act (F&DA) Health Canada holds final authority in the regulation of pharmaceutical promotion. In practice, however, the regulatory functions pertaining to the oversight of PSR promotion are delegated to two non-governmental organizations: the Pharmaceutical Advertising Advisory Board (PAAB), which evaluates written, broadcast and electronic promotional materials used

by PSRs; and Canada's Research-Based Pharmaceutical Companies (Rx&D), whose Code of Ethical Practices governs the verbal messages and ethical practices (e.g., gift-giving) of PSRs from member companies. PSRs from non-Rx&D and generic companies are excluded from this framework, although they are strongly encouraged by Health Canada to submit their promotional materials to PAAB for review, and the Canadian Generic Pharmaceutical Association has a Code of Marketing Conduct. Overall, the regulatory framework in Canada is largely one of self-regulation, with the possibility of government involvement in cases of serious complaints or violations of the laws and codes governing promotional practices.

***i. Food and Drugs Act (F&DA)***

Administered by Health Canada, the F&DA defines "advertising" as "any representation, by any means whatsoever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device" (89). The pharmaceutical sales visit is understood to be part of this definition.

The F&DA also sets out the basic criteria for acceptable pharmaceutical advertising. In particular, section 9 of the F&DA prohibits advertising of any drug that is "false, misleading, or deceptive; or is likely to create an erroneous impression regarding the character, the value, the quantity, composition, merit, or safety of the product" (89).

There is no formal monitoring of pharmaceutical promotional practices by Health Canada. Complaints that arise from one company concerning the promotional practices of another, or from an infringement noticed by a healthcare practitioner, are dealt with by the agency or organization that is most immediately involved in the oversight of the promotional practice in question (i.e., PAAB or Rx&D; roles

described further below). These cases may be referred to Health Canada when no resolution can be achieved at earlier stages. Enforcement measures taken by Health Canada are not publicized.

***ii. Pharmaceutical Advertising Advisory Board (PAAB) Code of Advertising Acceptance***

The PAAB is a non-governmental advertising clearance agency led by a Board of Directors composed of members representing various Canadian health and pharmaceutical associations and organizations, including Rx&D. Health Canada acts an external observer and advisor to the Board. The PAAB is responsible for reviewing promotional materials (any variety of communication media, including sales visit aids, journal advertisements, and internet advertisements) targeting healthcare professionals. The PAAB is financed entirely by fees collected from companies submitting advertisements for preclearance.

The PAAB Code sets the informational and audio-visual requirements that must be present in promotional materials in order to obtain approval for dissemination (90). Promotional materials reviewed under the PAAB Code must be accurate, complete, and clear, and designed to promote credibility and trust. Moreover, the promotional materials must provide sufficient information to permit assessment of harms and benefits in a prominent manner. Promotional materials must be consistent with Health Canada's approved product information. Off-label promotion is prohibited. However, the PAAB Code does not require advertisements to explicitly state that the drug was approved only on the basis of surrogate outcomes unless that information is contained in the Product Monograph (91).

Submission of promotional materials for review and clearance by PAAB is

voluntary. As a condition of Rx&D membership, however, companies must submit their promotional materials for review. Where generic pharmaceutical companies, or non-Rx&D-member companies are concerned, submission to PAAB is also strongly recommended by Health Canada, but not required. Once submitted, PAAB reviewers undertake an *a priori* review of the promotional materials according to the provisions of the PAAB Code. There is no formal monitoring of compliance with the PAAB Code. However, complaints regarding a company's promotional practices may be received either from competitors or from healthcare professionals. They are dealt with in a two-stage process, where first the PAAB writes to the company in question citing the complaint, and forwards the company's response to the complainant. If the complainant remains unsatisfied, the PAAB Commissioner then rules on the complaint, and where the Commissioner finds against a company that refuses to cooperate, the matter is referred to Health Canada.

***iii. Canada's Research-Based Pharmaceutical Companies Code of Ethical Practices***

The Rx&D Code of Ethical Practices applies to member companies, and governs the activity of their PSRs. The Rx&D Code describes the information that should be present in verbal or other non-material messages disseminated by PSRs. In particular, it states that PSRs of member companies must provide "...full and factual information on products, without misrepresentation or exaggeration. Statements must be accurate and complete. They should not be misleading either directly or by implication"(92). The Rx&D Code also prohibits discussions of off-label or unapproved drug uses during promotional activities. These informational requirements, however, are not further clarified by guidance documents.

PSR training and educational requirements are also set in the Rx&D Code.

PSRs of member companies must complete, within two years of employment, an accreditation course offered by the Council for Continuing Pharmaceutical Education (a non-profit organization created by Rx&D and largely financed by research-based pharmaceutical companies operating in Canada). The course is comprised of 250-300 hours of study divided into two units: 1) Anatomy and Physiology, and 2) Pathophysiology and Pharmacology. At the end of the course, 1 multiple-choice exam is taken with a minimum passing grade of 60%. PSRs of member companies must have a sufficient level of knowledge about the general sciences and product-specific information. PSRs must also be trained on the applicable laws and regulations governing PSRs' interactions with health care professionals.

Compliance with the Rx&D Code is ensured through an agent of the member company, who must annually provide written acknowledgement to Rx&D that policies and procedures are in place to properly implement the Code of Ethical Practices. The Industry Practices Review Committee investigates complaints regarding a company's promotional practices. If found by the Committee to be in violation of the Code of Ethical Practices, the infringement may be published on the Rx&D website, though a previous analysis of Rx&D's publication of violations found deficiencies in the level of detail provided (93). A financial penalty ranging from $25,000 CAD to $75,000 CAD is applied. The matter may be further referred to the Rx&D Board of Directors.

### 1.3.2. Regulation of the pharmaceutical sales visit in France

The French regulatory framework involves multiple actors, including two branches of government, a non-government organization, and the industry itself.

***i. Public Health Code***

The Public Health Code provides the basis for the regulation of pharmaceutical promotion. Article L.5122-1 of the Public Health Code defines "pharmaceutical advertisement" as "any form of information including canvassing, prospecting or enticement with the aim of promoting the prescription, delivery, sale or consumption of medicinal products" with the exception of pharmacists who provide information as part of their professional practice (94). The sales visit is understood to be part of this definition.

The Public Health Code also highlights the informational requirements in advertising and procedures to attain approval for dissemination of advertising material. Article L.5122-2 of the Public Health Code states that information in promotions must:

- not be misleading or jeopardize public health;
- be presented in an objective manner;
- be consistent with the appropriate use of the drug;
- be consistent with approved indications, and with the National Health Authority's therapeutic strategy recommendations.

The National Agency on the Safety of Medicines is responsible for implementing these regulations. In particular, prior to dissemination, the agency must review and approve according to the above criteria all promotional materials for drugs listed on the national health insurance schemes. If no response is given within two months of submission to the agency, the promotional material is *de facto* accepted. Once accepted, promotional materials can remain in circulation for a period of up to two years before requiring renewed approval. Should the drug be subjected to a

reassessment of its risk-benefit profile by the agency, stoppage of all promotional activities is required until reassessment is completed. Drugs that do not have reimbursement status are not required to submit promotional materials for review.

Violation of the Public Health Code is a criminal offence carrying a maximum fine of €37,500. Where the National Agency on the Safety of Medicines identifies an instance of non-compliance, it may request that the company modify its document or stop its dissemination. Lacking company cooperation, the agency can then impose a financial sanction of up to €10,000. Furthermore, where the agency has prohibited a promotion, the government pharmaceutical price-setting body (Comité économique des produits de la santé or CEPS) can also impose a financial penalty in the form of deducting up to a maximum of 10% of the company's turnover for 6 months before and after the infringement (95). Decisions made by the agency can be challenged in Administrative Courts.

***ii. Sales Visit Charter***

In 2004, the CEPS signed a contractual agreement with the national pharmaceutical industry syndicate (Les entreprises du médicament or LEEM) as part of an ongoing effort to encourage the appropriate use of medicines and reduce costs (96). Although not a legislative document, the Sales Visit Charter is sanctioned by article L.162-17-8 of the French Social Security Code, which called for collaboration between the two parties (CEPS and LEEM) to set benchmarks on the quality of PSR promotion in the form of a legally binding agreement. Two objectives are formally defined for the PSR in this Charter: the first, to promote medicines to health professionals, and the second, to contribute to the development of pharmaceutical

companies*.

The Charter outlines the expected responsibilities and ethical conduct of the PSR (including the banning of gifts, samples and food). In addition to the Public Health Code, the Charter also requires the provision of certain documents in each visit: the product monograph, and two official drug score sheets issued by the National Health Authority: the rating of the drug's therapeutic value (SMR) and added therapeutic value compared with other drugs for the same condition (ASMR). It also explicitly requires that information on drug harms be provided during the visit.

The Charter also requires PSRs to have a minimum of 3 years of university-level education, with the last year being devoted to a curriculum leading to a license to work as a PSR. The focus of the curriculum is on building health sciences and regulatory knowledge. Thus, PSRs representing member companies of the LEEM possess a relatively uniform level of qualifications.

***iii. Sales Visit Certification Procedure***

Charter compliance at individual companies is ensured by a sales visit certification procedure administered by the National Health Authority (97). The certification procedure requires that the company implement procedures (under the supervision of a head pharmacist) to meet the following sales visit criteria:

- PSRs possess the knowledge and skills needed to provide high quality information, both in written and verbal mediums;
- PSRs possess the information and resources needed to carry out their Sales Visit Charter missions;
- PSRs and their managers have the resources to comply with ethical rules;

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* The Charter does not elaborate on what is meant by "development" (i.e., economic or research development).

- Evaluation and monitoring of PSR practices.

Third party accreditation organizations grant certifications on an annual basis after auditing the implementation of these procedures by individual companies.

***iv. European Federation of Pharmaceutical Industries and Associations Health Care Professionals Code***

The LEEM abides by the European Federation of Pharmaceutical Industries and Associations Health Care Professionals Code (98). As the LEEM is a signatory of the Sales Visit Charter, the code of ethics directly relating to the practices of PSRs in France is contained within the Charter.

### 1.3.3. Regulation of the pharmaceutical sales visit in the United States

The FDA's Office of Prescription Drug Promotion is the central regulatory body charged with the oversight of all PSR activities. Jurisprudence and case law also play a role in interpreting provisions in the FDCA, and therefore, in defining the limits of regulatory functions. In addition to federal-level legislation and regulations, individual states may also have their own mix of policies and legislations covering specific aspects of PSR activity (e.g., gift giving, data mining on physician prescribing patterns and PSR education). Individual state legislations are beyond the scope of this thesis.

***i. Food, Drug and Cosmetic Act and the Code of Federal Regulations***

The *Food, Drug and Cosmetic Act* (FDCA) directly regulates all pharmaceutical promotion (99). The FDCA defines "promotional labeling", as information disseminated through the manufacturer or a third party, and consisting of written materials such as brochures, sales aids and mailing pieces (excluding the product label). General provisions describe the information that must be contained in

labeling. In particular, the FDCA prohibits the introduction of a drug into interstate commerce that has not been approved by the FDA or that has been misbranded.

Title 21 of the FDCA's accompanying Code of Federal Regulations contains within it detailed requirements and clarifications of the articles contained in the FDCA (100). The Code of Federal Regulations also interprets verbal messages, including those disseminated by the PSR, as promotional labeling (101).

Together the FDCA and the Code of Federal Regulations require that pharmaceutical promotion:

- Not be false or misleading;
- Have fair balance;
- Be consistent with approved product labeling or package insert;
- Only include claims substantiated by adequate and well-controlled clinical studies.

The Code of Federal Regulations clarifies that a promotion that is false, lacking in fair balance, or otherwise misleading, is one that "contains representation or suggestion, not approved for use in the labeling, that a drug is better, more effective...safer, has fewer or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence"(100). The fair balance provision is unique to the US, and its interpretation has been elaborated in guidance documents issued by the Office of Prescription Drug Promotion as well as court cases.

Although the FDCA does not explicitly ban off-label promotion, the Office of Prescription Drug Promotion has traditionally interpreted the FDCA provisions banning the introduction of an unapproved drug or misbranded drug into interstate commerce as the equivalent of a prohibition on off-label promotion. PSRs are

permitted to provide physicians with reprints of scientific articles discussing off-label drug uses. A recent US appellate court decision, however, has set a precedent that may have implications for the enforcement regulations on off-label promotion in the future. In *United States vs. Caronia,* pursuant to a First Amendment argument of free speech, the court maintained that the promotion of off-label uses of a drug should be permitted as long as those uses were not false or misleading as per the scientific literature. The appellate court holds jurisdiction over the States of Vermont, New York, and Connecticut. The regulatory implications of this decision remain to be seen.

The Office of Prescription Drug Promotion is responsible for reviewing the information in all promotional materials as per the FDCA and the Code of Federal Regulations. Companies must submit all final promotional materials for prescription drugs to the Office at the time of dissemination to the public or health professionals. Review of materials is thus carried out *a posteriori*. Elsewhere, it has been acknowledged that staff at the Office cannot review all submissions received due to sheer volume (over 70,000 promotional pieces per year) (76).

The Office has several active monitoring strategies. Staff can attend continuing medical education and scientific conferences to monitor compliance with regulations. Complaints can be received from drug companies, healthcare professionals, consumers, or former drug company personnel. The Bad Ad program is an ongoing FDA-sponsored outreach program to educate and raise awareness among healthcare professionals about their role in helping to identify false or misleading pharmaceutical promotion. Healthcare professionals who believe they have identified a false or misleading promotion can reach the Bad Ad program at its phone and email coordinates.

When a promotional message in any medium (written or oral) is found to be in violation of the FDCA, the Office can take several enforcement actions, including the public posting of letters containing notices of violation (known as regulatory letters) to the company, seeking injunctions or decrees of consent, pursuing criminal action, or imposing civil and monetary penalties. Violations are most often seen in the form of omissions of risk information, misleading communication of indications, and the overstatement of product efficacy (76,102).

***ii. False Claims Act***

The judicial pathway to enforcement also plays a major role in the detection of violations and enforcement. In cases of company non-compliance, the Office of Prescription Drug Promotion may refer the matter to the US Department of Justice, where it will undergo further analysis and potentially lead to a government-initiated lawsuit against the company. The *False Claims Act* provides US citizens, federal, and state governments with the means to take legal action against companies for false or misleading promotions, particularly where claims may have defrauded government-run programs (as in the case of prescriptions being filled by government-sponsored Medicare and Medicaid programs). The False Claims Act is typically invoked in lawsuits involving whistleblower complaints against pharmaceutical promotional practices (103). If, upon investigation, the Department of Justice chooses to pursue legal action, whistleblowers are compensated with a percentage of the potential settlement.

### 1.3.4. Comparing regulations in Canada, France, and the United States

Sections 1.3.1 to 1.3.3 provided an overview of the regulatory frameworks on pharmaceutical promotion in each country, and established that variation exists in

terms of how each country approaches the same regulatory issue. Table 1 summarizes these comparisons.

The Canadian regulatory framework is mainly one of self-regulation, with Health Canada holding final authority on the governance of pharmaceutical promotion, but rarely intervening in practice. Moreover, in Canada, sales visit promotional materials and verbal messages are governed by two separate entities and their voluntary codes, one of which is self-regulatory (Rx&D and the Code of Ethical Practices). Enforcement of either code is passive, with violations being addressed only if a complaint has been made. In terms of enforcement, either the measures taken are relatively weak (e.g., publication of the type of infringement by a company in Rx&D newsletters), or they rarely enter the public sphere. Although the PAAB does not levy financial penalties for violations of its code, Rx&D may levy a sliding scale of financial sanctions on non-compliant member companies.

The regulatory frameworks in France and the US both have direct government involvement. In France, branches of government and non-governmental actors are involved in the regulatory framework, providing various avenues for oversight. However, the National Agency on the Safety of Medicines primarily oversees promotional activities, and possesses the legal authority to impose sanctions on companies in violation of promotional regulations. Substantial efforts are also made on the part of the industry to collaborate with government in defining the roles and responsibilities of the PSR.

The US has primarily centralized the regulatory functions pertaining to PSR promotion to the OPDP. In cases of non-compliance, the FDA publishes warning letters specifying the company and nature of violations on its website, along with the

offending materials (if applicable). It also requires the issuance of corrective messages sent to the target audience by the offending company for serious offences. The judicial pathway to enforcement is also more prominent in the US, significantly increasing the visibility of violations to the general public, and potentially resulting in large settlements that can be both financially deleterious and a setback to company reputation.

**Table 1 Comparison of sales visit regulations in Canada, France, and the US***

| | Canada | France | US |
|---|---|---|---|
| **General approach to regulation** | Self-regulation | Regulation by government drug agency. Sales visit certification procedures | Regulation by government drug agency |
| **Submission of promotional materials** | Voluntary but a condition of membership in Rx&D | Required | Required |
| **Mechanism of review of promotional materials** | A priori | A priori | A posteriori |
| **Information required in promotion** | Consistency with product label; no off-label promotion | Consistency with product label; no off-label promotion; therapeutic value of the drug | Consistency with product label; no off-label promotion (article reprints allowed); fair balance of benefits and harms |
| **Education and training** | Post-hiring certification course | Pre-hiring PSR-specific diploma | No formal requirements. Various State initiatives |
| **Monitoring** | PAAB reviews complaints on promotional material; Rx&D reviews complaints on activities | Ongoing certification of company sales visit procedures and practices | FDA reviews all PSR promotion complaints. Bad Ad Program. Some in-the-field monitoring. |
| **Enforcement** | Voluntary compliance. Small fines. | Voluntary compliance. Enforcement notices. Warnings. Ban of | Voluntary compliance. Public regulatory letters. Warning letters. |

| | | | |
|---|---|---|---|
| | | advertisement with or without penalties. | Corrective messages disseminated. Civil/criminal lawsuits and fines. |

*Adapted from Guénette L, Mintzes B. Pharmaceutical sales representatives' activities in Canada, France and the U.S. : opinions of key stakeholders on the effectiveness of current regulatory practices. J Popul Ther Clin Pharmacol, 2011; 18 (2):e204-5.

### 1.4 Information provided during sales visits in Canada, France, and the US

In 2009-2010, a prospective cohort study of primary care physicians in Vancouver, Montreal, Sacramento, and Toulouse used self-administered questionnaires to examine the content of information provided in the sales visit (1). The study represented the largest sample of physician self-reports used to date to identify the information presented in sales visits. It was also the first study to compare sales visit activity in the same time period across three different countries. The main objective was to determine whether country of origin (Canada, France, or the US) influenced how often physicians reported the provision of "minimally adequate safety information" (defined as mention of at least one approved indication, one serious adverse event, one common non-serious, adverse event, one contraindication, and no unapproved indications or unqualified safety claims) in the sales visit. It was hypothesized that minimally adequate safety information would be reported most often in Toulouse (due to stricter information standards in France), and that harm information would be reported more often in promotions in Sacramento (due to FDA fair balance provisions), than the combination of promotions in Vancouver or Montreal. The main findings were that:

- Provision of minimally adequate safety information was reported in 1.7% of promotions across all sites;
- Drug benefit information was reported about twice as often as harm information across all sites;

- Mention of at least one drug harm was reported significantly more often in Toulouse (61%) than in either Sacramento (39%), or Vancouver and Montreal combined (34%);

- For drugs containing at least one serious adverse event in the approved product information, claims of such serious adverse events were rarely reported across all sites (6%).

Key sales visit messages (as identified by physicians) were also qualitatively analyzed, providing additional insight into sales visit claims. For instance, nearly all PSR claims about rosiglitazone, a drug approved on the basis of surrogate outcomes, were unsubstantiated claims of drug safety. Rosiglitazone was withdrawn from Europe and restricted in North American markets in 2010 due to serious cardiac safety problems (104).

### 1.5 Rationale

To help physicians make informed prescribing decisions, PSRs should present an account of drug efficacy, indications, and harms as approved by national regulators. Drugs approved on the basis of surrogate outcomes merit a more thorough and careful analysis of the benefits and harms involved in their use. It is especially important to avoid making inferential leaps about the efficacy of these drugs.

A search on EMBASE using the terms (exp Drug Industry AND exp Drug Information AND (exp prescription/ or exp prescription drug)) informed us that no study had yet attempted to describe the efficacy information discussed in pharmaceutical sales visits specifically for drugs approved on the basis of surrogate outcomes.

### 1.6 Research questions

There were two main research questions in this thesis:

1) Is there a difference in the frequency of physician-reported claims of serious morbidity or mortality benefit in promotions for cardiovascular drugs approved on the basis of surrogate outcomes (where efficacy claims are therefore *unwarranted*) and promotions for cardiovascular drugs approved on the basis of serious morbidity or mortality outcomes (where efficacy claims are *warranted*)?

2) For promotions of cardiovascular drugs approved on the basis of surrogate outcomes only, is there a difference in the frequency of physician-reported claims of serious morbidity or mortality benefits (i.e., unwarranted efficacy claims) by country of promotion (Canada versus France versus US)?

We expected a lower frequency of promotions where physicians reported unwarranted drug efficacy claims, in line with regulations in all three countries requiring promotional claims consistent with approved product information. Of the three countries, we also predicted that unwarranted claims of drug efficacy would be reported least often in France, owing to French regulations requiring the provision of official documentation on drug efficacy and added therapeutic value during the sales visit.

## 2. METHODS

### 2.1 Data collection

This study was a subgroup analysis of the prospective cohort study described earlier (1). Between May 1 2009 to June 30 2010, primary care physicians from Montreal, Vancouver, Sacramento, and Toulouse were contacted in blocks of 25 from a randomized list of all physicians practicing in the relevant metropolitan area. In Montreal and Vancouver, the respective lists were obtained from the provincial college of physicians, in Toulouse, from the regional physicians' association (*Union Régionale des Professionnels de Santé - Médecins Libéraux - Midi Pyrénées*), and in Sacramento from independent physician associations (physicians practicing for Kaiser

Permanente and physicians affiliated with the University of California Davis do not see PSRs). Physicians were contacted over the period of 1 year to maximize participation. To be included in the sample, physicians were required to see PSRs in their regular practice, work at least 20 clinical hours per week, and serve a greater than 50% non-referral patient population. Members of advocacy groups with a focus on drug promotion, such as *Healthy Skepticism* or *No Free Lunch* were excluded, as were current employees of drug companies. Physicians were remunerated for their time with an honorarium equivalent to what they would receive from a brief consultation in the relevant metropolitan area.

A difference of 10% or more in the primary outcome (reporting of minimally adequate safety information) between sites was judged to be the minimum level affecting clinical practice. Taking into account the variability arising from the clustering of observations per physician, researchers aimed to enroll 65 physicians per site. 255 (36%) of those contacted were enrolled in the study. Figure 1 in Appendix A illustrates the recruitment process and participation results.

Physicians were instructed to record information about the visits they received as per usual practice over the course of 8 consecutive drug promotions using a questionnaire (see Appendix B). The questionnaire was adapted from similar instruments used in observational studies in France (73), and Australia and Malaysia (74), and pilot-tested in a sample of 15 physicians and 41 promotions in Victoria, British Columbia. The questionnaire was written in English and translated to French. Following translation, the written and online versions were tested for comprehension and timing. Fixed response and open response questions pertaining to the content and characteristics of the sales visit were included. Physicians were advised to fill the

questionnaire immediately after the sales visit. The unit of analysis was a drug-specific promotion where the PSR stated the name of a prescription-only drug and made at least one claim. If more than one drug was promoted during a single visit, each drug became the subject of a unique questionnaire.

Ethics approval for the original cohort study was obtained from the University of British Columbia behavioural ethics committee, the Ethics Committee of the Centre de recherche du Centre hospitalier de l'Université de Montréal (CR-CHUM), University of California at Davis, and the Union Régionale des Professionnels de Santé - Médecins Libéraux - Midi Pyrénées.

**2.2 Analysis**

In this subgroup analysis, the unit of analysis was a promotion where the physician reported at least one efficacy claim being made by the PSR about a specific cardiovascular drug.

**2.2.1. Independent variables**

There were two independent variables: 1) approved drug efficacy, and 2) the country of the sales visit.

*Approved drug efficacy*

We developed a binary independent variable describing two categories of drug promotions:

1) Promotion for a drug approved on the basis of surrogate outcome(s) ("surrogate outcome drug"); OR

2) Promotion for a drug approved on the basis of serious morbidity or mortality outcome(s) ("clinical outcome drug")

A "surrogate outcome" referred to a biomarker intended to substitute for a clinical endpoint and expected to predict clinical benefit (or harm or lack of benefit or

harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. A "serious morbidity or mortality outcome" referred to a fatal or non-fatal serious cardiovascular or cardiovascular disease-related outcome, and specifically: MI, stroke, coronary artery disease (CAD), HF, congestive heart failure (CHF), chronic stable angina, or renal disease.

Promotions were classified into either of these categories by consulting the approved product information about the promoted drug in the relevant national physician prescribing compendium, or online drug database available at the time of promotion (2009-2010). These were the 2009 and 2010 versions of the *Compendium of Pharmaceuticals and Specialties* in Canada, the 2009 and 2010 versions of *Le Guide Vidal* in France, and the online *Drugs@FDA* archives in the US. The efficacy outcomes for which a drug was approved by regulators may not have been synonymous with the total evidence available in the scientific literature at the time of marketing. Where an indication to prevent serious morbidity or mortality was first introduced during the study period, all promotions for the drug prior to the date of the added indication were classified as promotions for a surrogate outcome drug, and after that date as promotions for a clinical outcome drug[*].

*Country of sales visit*

There were four study sites: Montreal, Vancouver, Sacramento and Toulouse. We combined Montreal and Vancouver into one category to produce results for the three respective countries (Canada, France, and the US).

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[*] This occurred in one instance when rosuvastatin obtained FDA approval for the indication of reducing the risk of myocardial infarction in February 2010. Prior to this, the drug had only been approved for the reduction of lipid levels.

*Other explanatory variables*

The original cohort study also measured a set of physician, practice and sales visit variables (see Appendix E for a full list and definition of variables). Based on previous literature and logical considerations, seven variables were retained. Previous studies suggest that the frequency of sales visits received by physicians and physician attitudes towards pharmaceutical promotion can be influenced by the size of the physician's practice (i.e., number of physicians in the practice) (105,106), their affiliation with a medical faculty (105,107), and their volume of prescribing (105). The corresponding variables retained in analysis were: 1) the number of physicians practicing in the same setting, 2) whether the physician was affiliated with a medical faculty, and 3) whether the physician had previously prescribed the drug. It was also reasoned that the duration of the sales visit, the type of sales visit (one-on-one or group visit), the frequency of sales visits received, and whether this was the physician's first time receiving a promotion for the drug might impact the content of messages during promotion. The latter four variables were also retained in the analysis.

For the following variables, we used forward selection of variables on each outcome to determine whether the variable should be included in analysis: sex of physician, physician year of graduation, whether physician received funding by industry, and number of patients seen per week. A $p$ value of $<0.2$ was considered sufficient for variable inclusion. Appendix E lists the full set of variables, as well as the $p$ values obtained from univariate logistic regression.

In stratified analyses for promotions in France and the US, sample sizes were too small and quasi-separation of data was detected when all variables were included.

To mitigate, we ran cross-tab analyses for each outcome and explanatory variable to determine whether enough cases existed to warrant inclusion in outcome analysis. The variable of frequency of sales visits received was excluded in stratified analyses for France and the US on the basis of insufficient sample sizes.

**2.2.2. Dependent variable**

The dependent variable was dichotomized into whether or not the physician recalled at least one claim of drug efficacy on serious morbidity or mortality during the promotion. This information came from questionnaire item 7 which asked whether any beneficial drug effects were mentioned. If yes, the physician selected one or more of the following:

7a) drug effects on serious morbidity or mortality

7b) drug effects on quality of life

7c) drug effects on disease symptoms

7d) drug effects on asymptomatic physiological measures

7e) other, please specify

We examined the number of promotions where option 7a ("drug effects on serious morbidity or mortality") was selected. A promotion with a reported claim of drug efficacy on serious morbidity or mortality (7a) was coded as such regardless of all other responses given (7b to 7e). Promotions with no recalled claims of drug efficacy (i.e., a negative response to questionnaire item 7) were excluded from analysis. For lack of a second coder, we did not analyze open-text responses (7e). A reported claim of drug efficacy on serious morbidity or mortality was defined as an "unwarranted efficacy claim" when the promotion was for a surrogate outcome drug.

### 2.2.3 Analytical plan

We examined promotions of drugs indicated for cardiovascular or cardiovascular-related outcomes: anti-hypertensive, glucose-controlling, and lipid-lowering agents. Selecting this subset of promotions allowed us to make comparisons on the basis of different approved efficacy outcomes, while avoiding potential confounding in promotion information due to the products having different therapeutic goals. Tables 6 to 11 in Appendix C provide a list of study drugs and their summarized indications.

Two outcomes were examined:

1) Difference in the frequency of reported claims of serious morbidity or mortality benefit in promotions for drugs approved on the basis of surrogate outcomes (i.e., unwarranted efficacy claims) versus drugs approved on the basis of serious morbidity or mortality; AND

2) Difference in the frequency of reported claims of serious morbidity or mortality benefit in promotions for drugs approved on the basis of surrogate outcomes (i.e., unwarranted efficacy claims) in Canada, France, and the US.

For the analysis of the first outcome, we examined all cardiovascular promotions where at least one claim of drug efficacy was reported. For the analysis of the second outcome, we examined all cardiovascular promotions where at least one claim of drug efficacy was reported and the promoted drug was approved on the basis of surrogate otucomes. Appendix A illustrates the sample of promotions included in each outcome analysis.

We used the generalized estimating equations (GEE) for each outcome to carry out binary logistic regression while adjusting the odds ratio (OR) and confidence intervals (CI) to account for multiple responses from the same physician. SPSS version 21 (IBM) was used for all analyses. GEE parameters for these outcomes are

listed Appendix F.

*Missing values*

There were missing values in 27 (>0.1%) cases (see Appendix D for the list of variables with missing values). Since the sample size was limited, we maximized available data using multiple imputation runs on SPSS. All analyses were carried out using five sets of imputed data.

## 3. RESULTS

### 3.1 Sample

Overall, we included 448 promotions for 58 unique brand name drugs used to treat cardiovascular-related outcomes (see Appendix C for the drug list). These drugs were promoted to 196 physicians across the three countries (92 in Canada, 57 in France, and 47 in the US). The sample represented 26% of the 1692 promotions, and 77% of the 255 physicians included in the original cohort study. Tables 2 and 3 summarize the characteristics of the physicians and promotions included in the sample.

In this sample of promotions for cardiovascular drugs, physicians across all countries received between 1 to 7 promotions, with a median of 2 promotions per physician (interquartile range 1, 3). The majority of promotions (347 or 77%) were for drugs approved on the basis of surrogate outcomes: 157 (74%) promotions in Canada, 105 (79%) in France, and 85 (82%) in the US.

The majority of promotions (83%) were one-on-one visits to physicians. In 76% of promotions, the physician had previously received sales visits for the same drug, and in 67% the physician had previously prescribed the drug. More than half (61%) of promotions were longer than 5 minutes in duration.

**Table 2 Physician and practice characteristics**

| | Country* | | | |
|---|---|---|---|---|
| **Characteristic** | **Canada** N=92 | **France** N=57 | **US** N=47 | **Overall** N=196 |
| Median promotions per physician (interquartile range) | 2 (1,3) | 2 (1,3) | 2 (1,3) | 2 (1,3) |
| Male physician, n (%) | 56 (60.9) | 45 (78.9) | 34 (72.3) | 135 (68.9) |
| Mean year of physician graduation ± SD | 1984 ± 10 | 1984 ± 10 | 1989 ± 9 | 1985 ± 10 |
| Physician received PSR visits at least twice weekly, n (%) | 47 (51.1) | 50 (87.7) | 40 (85.1) | 137 (69.9) |
| Solo practice, n (%) | 20 (21.7) | 20 (57.1) | 11 (23.4) | 51 (26.0) |
| Mean patients seen per week ± SD | 131 ± 53 | 119 ± 40 | 98 ± 48 | 120 ± 50 |

*N represents the number of physicians per country or overall

**Table 3 Promotion characteristics**

| | Country * | | | |
|---|---|---|---|---|
| **Characteristic** | **Canada** N=211 | **France** N=133 | **US** N=104 | **Overall** N=448 |
| Promotions for surrogate outcome drugs, n (%) | 157 (74.4) | 105 (78.9) | 85 (81.7) | 347 (77.4) |
| Promotion ≤5 minutes, n (%) | 87 (41.2) | 37 (27.8) | 49 (47.1) | 173 (38.6) |
| One-to-one promotion, n (%) | 148 (78.3) | 130 (97.7) | 75 (72.1) | 371 (82.8) |
| First promotion received for drug, n (%) | 53 (25.1) | 35 (26.3) | 19 (18.3) | 107 (23.9) |
| Physician previously prescribed drug, n (%) | 155 (73.5) | 71 (53.4) | 71 (68.3) | 297 (66.3) |

*N represents the number of promotions per country or overall

## 3.2 Main outcomes

### 3.2.1 Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs

Table 4 compares the frequency of sales visit claims of serious morbidity or

mortality benefits recalled by physicians for surrogate outcome drugs versus clinical outcome drugs. The results are pooled for all three countries, and stratified for Canada, France, and the US. Overall, claims of serious morbidity or mortality benefits were reported in 156 (45%) of the 347 promotions for surrogate outcome drugs, constituting unwarranted efficacy claims. For the 101 promotions for drugs approved on the basis of serious morbidity or mortality, 72 (71%) were reported to have these same efficacy claims. In the pooled analysis, claims of serious morbidity or mortality efficacy were reported significantly more often in promotions for clinical outcome drugs than surrogate outcome drugs, adjusted OR=0.3 (95% CI 0.2, 0.6), $p<0.001$. In Canada, 72 (46%) promotions for surrogate outcome drugs were recalled with claims of serious morbidity or mortality benefits compared to 37 (68%) promotions for clinical outcome drugs, adjusted OR=0.5 (95% CI 0.2, 1.0), $p=0.07$. In France, claims of serious morbidity or mortality benefit were reported in 62 (59%) promotions for surrogate outcome drugs versus 24 (86%) promotions for clinical outcome drugs, adjusted OR=0.1 (95% CI 0.03, 0.8), $p=0.03$. Finally, claims of serious morbidity or mortality benefit were reported in 22 (26%) US promotions for surrogate outcome drugs compared to 11 (58%) promotions for clinical outcome drugs, adjusted OR= 0.3 (95% CI 0.1, 1.1), $p=0.07$.

**Table 4 Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs**

| | **Frequency of reported claims of serious morbidity or mortality benefit** | | | |
|---|---|---|---|---|
| **Country** | **Surrogate outcome drug promotions*, n/N (%)** | **Clinical outcome drug promotions§, n/N (%)** | **Surrogate versus clinical outcome promotions, adjusted OR (95% CI)** | ***p*** |
| **Canada** | 72/157 (45.9) | 37/54 (68.5) | 0.5 (0.2, 1.0) | *0.07* |
| **France** | 62/105 | 24/28 | 0.1 | *0.03* |

| | | | | |
|---|---|---|---|---|
| | (59.0) | (85.7) | (0, 0.8) | |
| **US** | 22/85<br>(25.9) | 11/19<br>(57.9) | 0.3<br>(0.1, 1.1) | *0.07* |
| **Overall** | 156/347<br>(45.0) | 72/101<br>(71.3) | 0.3<br>(0.2, 0.6) | *<0.001* |

*Defined as promotions for drugs approved on the basis of surrogate outcomes; N reflects the total number of promotions for drugs approved on the basis of surrogate outcomes in region.
§Defined as promotions for drugs approved on the basis of serious morbidity or mortality outcomes; N reflects the total number of promotions for drugs approved on the basis of serious morbidity or mortality in region.

### 3.2.2 Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate outcome drugs in Canada versus France versus US

Seventy-two (46%) Canadian promotions for drugs approved on the basis of surrogate outcomes were reported to have unwarranted claims of serious morbidity or mortality benefit, while this was the case for 62 (59%) French promotions, and 22 (26%) US promotions. The odds of a reported claim of serious morbidity or mortality benefit in promotions for surrogate outcome drugs were significantly higher in France compared to the US, adjusted OR= 3.9 (95% CI 1.6, 9.3), $p$=0.02. The odds of a reported claim of serious morbidity or mortality benefit were also marginally significantly higher in Canadian versus US promotions for surrogate outcome drugs, adjusted OR=2.4 (95% CI 1.0, 5.5), $p$=0.04. The comparison between French and Canadian promotions for surrogate outcome drugs was not significant, although claims of serious morbidity or mortality benefit were still reported more often in France, adjusted OR= 1.7 (95% CI 0.8, 3.3), $p$=0.2.

**Table 5 Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs in Canada, France and the US**

| | **Frequency of reported claims serious morbidity or mortality benefit in promotions for surrogate outcome drugs*** | | |
|---|---|---|---|
| **Countries compared** | **n (%)** | **Country versus country, adjusted OR (95% CI)** | ***p*** |

| | | | |
|---|---|---|---|
| **Canada versus France** | 72 (46) v. 62 (59) | 0.6 (0.3, 1.3) | *0.2* |
| **France versus US** | 62 (59) v. 22 (26) | 3.9 (1.6, 9.3) | *0.02* |
| **Canada versus US** | 72 (46) v. 22 (26) | 2.4 (1.0, 5.5) | *0.04* |

*Defined as promotions for drugs approved on the basis of surrogate outcomes

## 4. DISCUSSION

### 4.1 Unwarranted claims of drug efficacy during the sales visit

As predicted, the odds of a reported claim of serious morbidity or mortality benefit were significantly lower in promotions for surrogate versus clinical outcome drugs. Across all countries, promotions for clinical outcome drugs were reported to have made claims of serious morbidity or mortality benefit more often than promotions for surrogate outcome drugs, although the difference in the frequency of such claims was only significant in France. However, the claims of serious morbidity or mortality benefit reported in nearly half of all promotions for surrogate outcome drugs constituted unwarranted efficacy claims and off-label promotion. Such promotions would also be considered non-compliant with regulations in all three countries.

Inflated claims of drug efficacy have been identified medical journal advertisements in the US (71,108), Sweden (109), Spain (110), Australia and Malaysia (74). In an analysis of FDA warning letters to pharmaceutical companies for non-compliant promotions between 2000 to 2006, misleading or overstated efficacy claims constituted one of the top three (of 22) categories of violations (111). Compared to reports from the original cohort study on the promotion of unapproved indications, our findings suggest that unwarranted claims of drug efficacy (46% in Canada, 26% in the US to 85% in France) may be occurring much more frequently

than the promotion of unapproved indications (reported in 13% of promotions across all sites in the original cohort study) (1).

To our knowledge, this is the first study to report on claims of drug efficacy during the sales visit across several countries. We hypothesized that for promotions of drugs approved on the basis of surrogate outcomes, unwarranted claims of drug efficacy would be made least often in France owing to regulations that require the provision of official scoresheets rating the promoted drug's therapeutic value (SMR and ASMR). Since these documents compare and contextualize the drug's therapeutic benefit in relation to other treatment options, we reasoned that their provision in the sales visit would provoke a discussion of the drug's actual efficacy profile, and avoid unwarranted efficacy claims.

Our findings contradicted this hypothesis. Claims of serious morbidity or mortality were reported more often in French promotions for surrogate outcome drugs than promotions in Canada or the US, and differences were significant between France and the US. This may suggest an overall lack of adherence to French regulations requiring the provision of drug efficacy scoresheets, a finding that has been reported in several observational studies of regulatory compliance in France (73,112,113). It may also point to a cultural bias towards stronger claims of drug efficacy in French sales visits, or towards stronger interpretations of promotional efficacy messages by French physicians, as health benefits were also reported most often in French promotions (87%) compared to promotions in Canada or the US (75-81%) in the original cohort study.

Of the three countries, promotions for surrogate outcome drugs in the US had the lowest odds of reporting unwarranted claims of drug efficacy on serious morbidity

or mortality. The difference was significant between US and French promotions, and marginally significant between US and Canadian promotions. This finding may partly be explained by the publicized and financially burdensom government-led lawsuits in the US with sums significantly exceeding Canadian or French penalties. Nearly every major drug manufacturer in the US has now been touched by government investigation and prosecution for violation of the FDCA and the FDA's regulations on off-label promotion (114). On-the-other hand, repeated violations of promotional regulations despite financial penalties in the billions of dollars argue that very costly fines or direct regulatory oversight by the FDA may not be the only factors involved in the US. A further contributing factor may be the significant attention paid to the issue of physician interactions with industry and rational prescribing, by non-governmental organizations in the US. For instance, the American Medical Students Association releases annual scorecards rating academic medical centres in every State on the presence of absence of policies governing trainee and faculty interactions with industry (115). The National Physicians Alliance's Unbranded Doctor Campaign is another campaign providing physicians with the tools and resources to establish practices guarded from industry influence, and particularly from sales visit information (116). The combination of these advocacy campaigns, along with the fact that a substantial number of physicians in California already refuse or are forbidden from receiving sales visits (notably, physicians at Kaiser Permanente and University of California, Davis), may have had a neutralizing effect on the information provided in the sample of US promotions examined in this study.

In Canada, one 1998 study examined enforcement procedures at the Pharmaceutical Manufacturers' Association of Canada (now Rx&D), where the

industry association maintained a policy of publishing violations of the Code of Ethical Practices in the industry newletter *PMAC News* (93). Lacking from these publications were the details on nature of the infringement, and the value of sanctions imposed. There have been no more recent evaluations of performance in this area of regulation in Canada. In particular, such studies are challenging to produce in the Canadian context given Health Canada's lack of transparency in outlining the enforcement steps taken when faced with non-compliant company promotion. The results of this study and the findings from the original cohort study however suggest that regulations may still be loosely adhered to in Canada.

**4.2 Limitations**

The findings in this study are from the primary care setting and cannot necessarily be generalized to sales visits received by specialists or other healthcare professionals, such as nurses or pharmacists. We also relied on physician reports of claims made by PSRs. Physicians themselves could have made unwarranted inferences about the efficacy messages conveyed during promotion, and these inferences may have been facilitated through other aspects of the sales visit, such as whether small gifts or samples were involved. However, the messages that physicians take away from the sales visit ultimately form the basis of prescribing decisions. Moreover, the pragmatic nature of this study allowed for sales visits to take place naturally, whereas informing sales representatives that interactions were being recorded may have led to observer effect bias. The original cohort study also did not distinguish between spontaneously volunteered information and information provided upon further prompting. Further research may be necessary to understand how physicians process and interpret the information provided in sales visits, and the

translation of this information into clinical decision-making.

We also encountered difficulty categorizing some of the oral antidiabetics (in particular metformin, and the insulins) as either drugs approved on the basis of surrogate, or serious morbidity or mortality outcomes. Examination of the indications contained in pharmaceutical compendia and government drug databases in the three countries revealed that all antidiabetic drugs examined were approved to improve glycemic control in type 2 diabetes patients (a surrogate outcome). This highlights a general difficulty with product monographs and related regulatory documents: they lack a standardized and informative presentation of the evidence on drug efficacy, and appropriate usage.

Second, this study was a secondary analysis of previously collected data, and answers to the research questions could not be collected in the most fulsome or direct manner. For instance, item 7 of the original cohort study questionnaire allowed us to investigate the category of efficacy claim (i.e., a claim of drug efficacy on serious morbidity or mortality), but not the exact efficacy claims were being recalled in each promotion. With such detail, one could avoid relying on physician interpretations of the category into which an efficacy claim would fall.

The data in this study were also collected in the midst of a public health scandal involving the off-label promotion of Servier's amphetamine derivative benfluorex (Mediator) in France. Approved as an adjunct to diet and exercise for the treatment of diabetes, benfluorex was nevertheless marketed more generally for weight loss (117). By market withdrawal in 2009, there were an estimated 1300 deaths and over 3000 hospitalizations attributed to the cardiotoxicity properties of the drug (118). This provoked a national investigation (119) and a reform of French drug

regulations, including regulations governing pharmaceutical promotion. Subsequent changes included an updated version of the Sales Visit Charter (which now requires the establishment of a national observatory on the sales visit, and annual evaluations of PSR knowledge on scientific and regulatory topics) (120) and a strengthening of the national drug agency's ability to impose financial sanctions on companies for non-compliance. The changes implemented since the study data collection may have improved the quality of efficacy messages in French promotions.

Finally, the generalizability of our results is limited as our sample represented only four cities in three countries (Toulouse, Sacramento, Vancouver and Montreal). The number of observations, particularly for French and US promotions, were also limited. As such, it was not possible to adjust the odds ratios in the stratified analyses of promotions in these two jurisdictions with the full set of variables planned for GEE analysis (the "frequency of sales visits received" was excluded as noted in Appendix E).

### 4.3 Implications of study

In general, the results of the original cohort study and this subgroup analysis suggest that while regulatory measures may have a modest impact on sales visit practices, this impact may not be easily deduced from the stringency of formally written laws, regulations and guidelines. There may be discrepancies between the intent and the practical implementation of regulations.

To better understand how regulations affect sales visits in practice, it may also be informative to turn to qualitative studies engaging regulatory officials and stakeholders in a discussion of the practical barriers and enablers encountered in regulation. Our results suggest that despite the diversity of approaches to regulation,

inflated claims of drug efficacy are reported across all countries. Common barriers to regulating the sales visit may therefore be experienced in each country. Given their proximity to the regulated activity, it may be plausible for regulators (i.e., drug agencies) to produce field audits of sales visit practices at regular time intervals. As a first step, however, transparency of regulatory processes (e.g., enforcement actions) could enhance accountability of both regulators and companies, and serve as a detterent to non-compliant activities before any other enforcement action is taken.

Since the goal of sales visit regulations is to protect public health (42), regulation may ultimately be one aspect of a multi-pronged strategy aiming to curb industry influence and improve rational prescribing. Interventions that could complement regulation include policies on interactions with the pharmaceutical industry in academic medical centres and managed care organizations (121), education to raise awareness of industry influence as early as medical school (122) (123), and countervailing of industry messages through educational outreach visits (or academic detailing) (124).

## 5. CONCLUSION

Claims of efficacy made in sales visit promotions for drugs approved on the basis of surrogate outcomes were frequently misleading in that they extended beyond the regulator-approved efficacy information for the product. The frequency of unwarranted claims of serious morbidity or mortality benefit varied by country, although the observed differences did not reflect our analysis of regulation stringency. Unwarranted claims of drug efficacy constitute a form of off-label promotion, contravene national regulations in most countries, and therefore merit greater attention from regulators.

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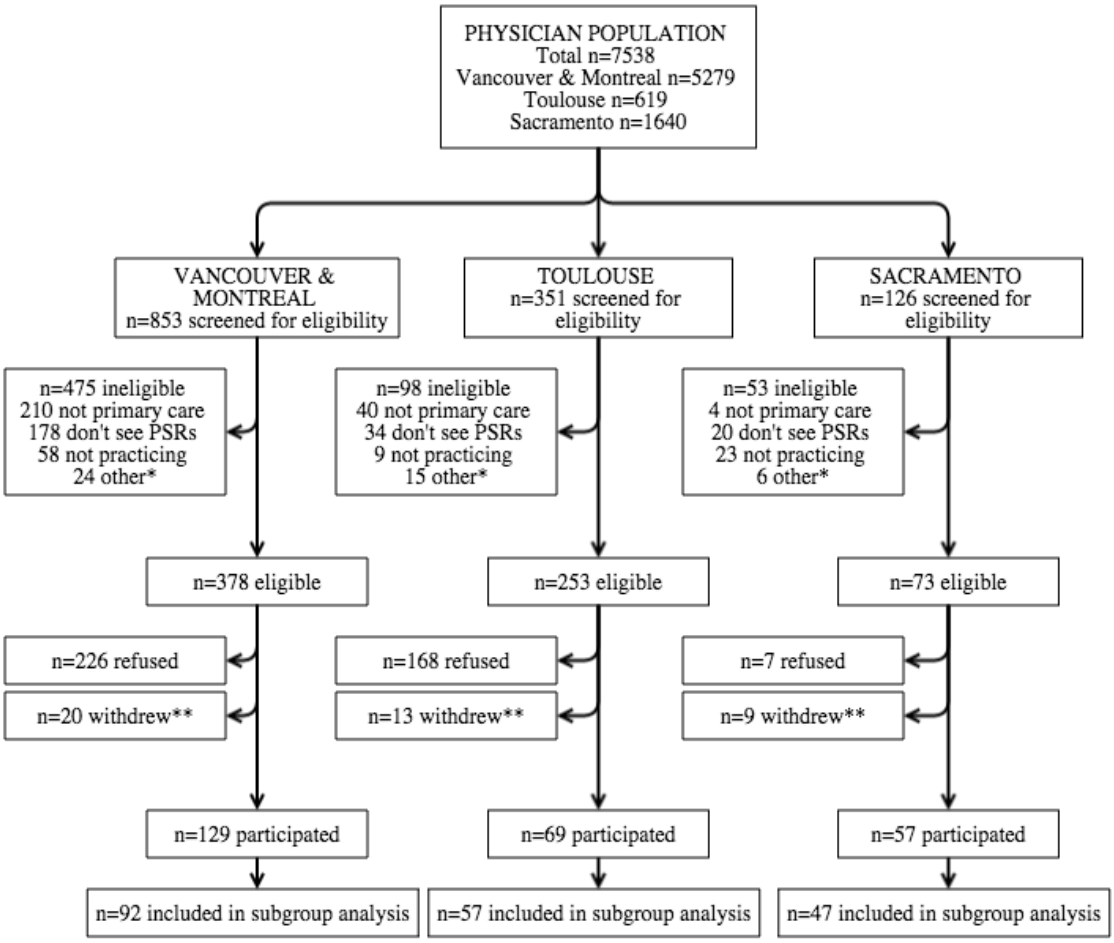
# APPENDICES

## Appendix A - Physician and promotion sample inclusion

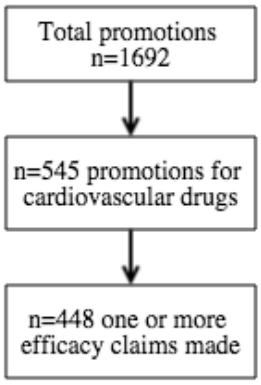
**Figure 1** Physician recruitment, participation and selection




Adapted from Mintzes B, Lexchin J, Sutherland JM, Beaulieu M-D, Wilkes MS, Durrieu G, et al. Pharmaceutical sales representatives and patient safety: A comparative prospective Study of information quality in Canada, France and the United States. J Gen Intern Med. 2013;28(10):1368–75

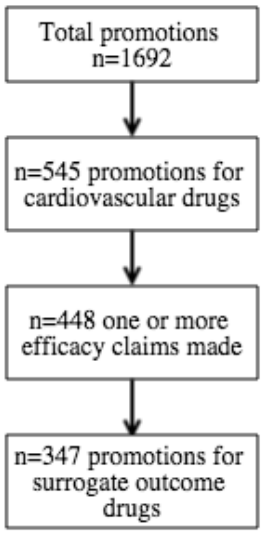
*"other" includes maternity leave, sick leave, deceased, and unspecified
** Physicians who withdrew before filling in any questionnaires
NOTE: Vancouver and Montreal primary care physician lists obtained from British Columbia and Québec College of Physicians. Toulouse list from the Union régionale des professionnels de santé - médecins libéraux - Midi-Pyrénées. Of the 4380 phyisicians licensed to practice in Sacramento, estimated 37% are primary care physicians (US physician workforce data: http://bhpr.hrsa.gov/healthworkforce/allreports.html)

**Figure 2** Sample of promotions included in analysis of outcome 1*




*Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs

**Figure 3** Sample of promotions included in analysis of outcome 2**




**Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate outcome drugs in Canada versus France versus US

# Appendix B - Physician questionnaire

**Physician code:** | | | | | | | |

## Pharmaceutical Sales Representatives and Patient Safety Questionnaire

**PLEASE FILL IN ONE FORM FOR EACH PROMOTED MEDICINE**

**Date (month/day/year):** m m / d d / 2 0 0 9

**Name of the drug:** _____

**Is this the first time this drug has been promoted to you by a sales representative?**

❍ Yes ❍ No

**Was this visit?**

❍ one-to-one
❍ a group session including other physicians

**How long did the visit last?**

❍ 5 minutes or less
❍ 6 to 10 minutes
❍ 11 to 20 minutes
❍ more than 20 minutes

**INFORMATION ON THE PROMOTED DRUG - BENEFITS AND HARM**

**1. Did the sales representative mention any indications for use?**

❍ Yes ❍ No

→ ***If yes, please list all indications that were mentioned:***

**2. Did the representative mention specific groups of patients for whom this drug is indicated?**

❍ Yes ❍ No

→ ***If yes, please list:***

**3. Did the representative mention specific groups of patients for whom this drug is contraindicated?**

❍ Yes ❍ No

→ ***If yes, please list:***

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**4. Were any adverse effects mentioned?**

❍ Yes ❍ No ⟶ ***If no, go to question 6***

***If yes, how would you describe these adverse effects? (please check all that apply)***

- ❍ 4a. serious adverse events (life-threatening, leading to hospitalization and/or to ongoing disability)
- ❍ 4b. common non-serious symptomatic adverse effects (e.g., nausea, dizziness, bloating, etc)
- ❍ 4c. adverse effects involving specific groups of patients
- ❍ 4d. dose-related adverse effects
- ❍ 4e. adverse effects related to drug interactions
- ❍ 4f. laboratory test results indicating harm
- ❍ 4g. other

***Please list all adverse effects mentioned:***

**5. Was the likelihood or magnitude of harm described?**

❍ Yes ❍ No

***If yes, indicate the type of information provided:***

- ❍ 5a. absolute numbers of patients (e.g., 20% of treated patients experience dizziness)
- ❍ 5b. relative risk increases (e.g., leads to a doubling of risks of kidney failure)
- ❍ 5c. other, *please specify:*

**6. Were any safety claims made?**

❍ Yes ❍ No

***If yes, were they? (please check all that apply):***

- ❍ 6a. unqualified claim (e.g., “this drug is safe”)
- ❍ 6b. qualified claim (e.g., ‘’well-tolerated’’ or ‘’few side effects”)
- ❍ 6c. comparative claim (e.g., better tolerated than drug xx)
- ❍ 6d. other, *please specify:*

**7. Did the representative provide information on the drug's beneficial effects?**

❍ Yes ❍ No ⟶ ***If no, go to question 9***

***If yes, how would you describe these drug benefits? (please check all that apply)***

- ❍ 7a. effects on serious morbidity or mortality
- ❍ 7b. effects on quality of life
- ❍ 7c. effects on disease symptoms
- ❍ 7d. effects on asymptomatic physiological measures (e.g., cholesterol, bone density, etc.)
- ❍ 7e. other, *please specify*:

**8. Was the likelihood or magnitude of benefit described?**

❍ Yes ❍ No

***If yes, indicate the type of information provided:***

- ❍ 8a. absolute numbers of patients (e.g., out of every 100 patients treated, 10 improved)
- ❍ 8b. relative risk reductions (e.g., leads to a 50% reduction in heart attack risk)
- ❍ 8c. differences in an evaluation score (e.g., a 10 point reduction in pain scores)
- ❍ 8d. other, *please specify*:

**9. Was the drug's pharmacology described?**

❍ Yes ❍ No

***If yes, was this?***

- ❍ 9a. the mechanism of action
- ❍ 9b. how the drug is handled by the body (pharmacokinetics)
- ❍ 9c. the drug class (e.g., ace inhibitor, calcium channel blocker)
- ❍ 9d. other, *please specify:*

**PAYMENT**

**10. Did the representative mention the drug's cost to consumers?**

❍ Yes ❍ No

→ ***If yes, was this in comparison with another drug?***

❍ Yes ❍ No

→ ***Which drug or drugs?***

**11. Did the representative discuss reimbursement by public or private insurers?**

❍ Yes ❍ No

→ ***If yes, what was said?***

**GENERAL CLAIMS**

**12. Were any statements made about cost-effectiveness?**

❍ Yes ❍ No

**13. Was another clinician's favourable opinion of the drug stated?**

❍ Yes ❍ No

→ ***If yes, was this? (please check all that apply)***

- ❍ 13a. another family physician
- ❍ 13b. a local specialist clinical expert
- ❍ 13c. a national or international expert
- ❍ 13d. other, *please specify*:

**14. Overall, what was the sales representative's key message about the drug?**

**14a. In your opinion, how accurate was this key message?**

❍ 95% or more ❍ 75% ❍ 50% ❍ 25% ❍ 5% or less ❍ Not applicable

**ADDITIONAL MATERIALS PROVIDED**

**15. Did the sales representative provide you with any article reprints?**

❍ Yes ❍ No ⟶ ***If no, go to question 17***

***If yes, did this include? (please check all that apply)***

- ❍ 15a. randomized controlled trial reports, meta-analyses or systematic reviews
- ❍ 15b. general review articles
- ❍ 15c. clinical guidelines
- ❍ 15d. conference or symposium reports
- ❍ 15e. other, *please specify:*

**16. Why were reprints provided? (please check all that apply)**

- ❍ 16a. to support claimed effectiveness and/or safety
- ❍ 16b. to refute negative evidence on safety or effectiveness
- ❍ 16c. other, *please specify*:

**17. Were any patient brochures or teaching aids provided?**

❍ Yes ❍ No

**18. Was government approved product information provided? (e.g., drug data sheet or monograph)**

❍ Yes ❍ No

**18a. If no, was other prescribing information provided? (including, for example, starting dose, any titration, duration of therapy, route of administration, etc.)**

❍ Yes ❍ No

**19. Did the representative give you any promotional items or samples?**

❍ Yes ❍ No

***If yes, did this include? (please check all that apply)***

- ❍ 19a. free samples of drugs
- ❍ 19b. pens, notepads, or prescription pads
- ❍ 19c. a lunch or other food provided by the representative
- ❍ 19d. other offers of promotional items, gifts, or social invitations

***If other, please list:***

**20. Were you invited to an event that the company either directly funded or that was paid for by an educational grant from the company? (e.g., medical education program, dinner, conference, symposium, advisory board, speaker's panel)?**

❍ Yes ❍ No

→ ***If yes, please specify:***

**21. Were you invited to participate in a study or recruit patients for a study?**

❍ Yes ❍ No

→ ***If yes, briefly describe, including whether this is a study of a drug that is already on the market or a drug that the company hopes to market in the future:***

***21a. Did you agree to participate?***

❍ Yes ❍ No ❍ Undecided

**OVERALL ASSESSMENT**

**22. In general, how would you rate the quality of the scientific information presented by the representative?**

❍ excellent ❍ good ❍ fair ❍ poor ❍ very poor

**23. Have you previously prescribed this drug?**

❍ Yes ❍ No

**24. How likely are you to start or to increase your prescribing of this drug compared with before the visit?**

❍ very likely ❍ somewhat likely ❍ somewhat unlikely ❍ very unlikely

**Do you have any comments?**

**Thank you very much for your assistance!**

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## Appendix C - Generic name, indications, and frequency of promoted drugs

**Table 6 Generic name, indications, and frequency of promoted surrogate outcome drugs in Canada**

| Generic Name | Indication(s) | Frequency |
|---|---|---|
| Aliskiren | Hypertension | 7 |
| Candesartan/hydrochlorothiazide | Hypertension | 1 |
| Ezetimibe | Lipid control | 17 |
| Fenofibrate | Lipid control | 4 |
| Gliclazide | Diabetes in adults | 3 |
| Hydrochlorothiazide/losartan | Hypertension | 2 |
| Hydrochlorothiazide/ramipril | Hypertension | 1 |
| Insulin glulisine | Types 1 and 2 diabetes | 1 |
| Insulin detemir | Types 1 and 2 diabetes | 1 |
| Insulin lispro/insulin lispro protamine | Diabetes | 2 |
| Metformin/sitagliptin | Type 2 diabetes | 5 |
| Nicotinic acid | Lipid control | 8 |
| Olmesartan | Hypertension | 15 |
| Perindopril/indapamide | Hypertension | 6 |
| Rosiglitazone | Type 2 diabetes | 5 |
| Rosuvastatin | Lipid control | 29 |
| Saxagliptin | Type 2 diabetes | 16 |
| Sitagliptin | Type 2 diabetes | 17 |
| Telmisartan | Hypertension | 17 |

**Table 7 Generic name, indications, and frequency of promoted clinical outcome drugs in Canada**

| Generic Name | Indication(s) | Frequency |
|---|---|---|
| Amlodipine/atorvastatin | CAD risk | 2 |
| Atorvastatin | Lipid control; MI & stroke risk | 3 |
| Candesartan | Hypertension; HF | 3 |
| Irbesartan | Hypertension; Renal disease | 11 |
| Nifedipine | Chronic stable angina; Hypertension | 1 |
| Perindopril | Hypertension; HF; CAD risk | 19 |
| Quinapril | Hypertension; CHF | 1 |
| Trandolapril | Hypertension; Post-MI | 12 |
| Valsartan | Hypertension; CAD risk; HF | 2 |

**Table 8 Generic name, indications, and frequency of promoted surrogate outcome drugs in France**

| Generic Name | Indication(s) | Frequency |
|---|---|---|
| Aliskiren | Hypertension | 17 |
| Amlodipine/olmesartan | Hypertension | 9 |
| Amlodipine/valsartan | Hypertension | 2 |
| Candesartan/hydrochlorothiazide | Hypertension | 2 |
| Enalapril/lercanidipine | Hypertension | 11 |
| Exenatide | Type 2 diabetes | 3 |
| Ezetimibe | Lipid control | 1 |
| Ezetimibe/simvastatin | Lipid control | 3 |
| Fenofibrate | Lipid control | 3 |
| Hydrochlorothiazide/olmesartan | Hypertension | 1 |
| Hydrochlorothiazide/valsartan | Hypertension | 2 |
| Insulin detemir | Diabetes in adults and children | 1 |
| Insulin glargine | Diabetes in adults and children | 1 |
| Losartan/hydrochlorothiazide | Hypertension | 1 |
| Manidipine | Hypertension | 1 |
| Metformin | Type 2 diabetes | 1 |
| Metformin/pioglitazone | Type 2 diabetes | 1 |
| Metformin/sitagliptin | Type 2 diabetes | 3 |
| Metformin/vildagliptin | Type 2 diabetes | 16 |
| Olmesartan | Hypertension | 4 |
| Rosuvastatin | Lipid control | 7 |
| Saxagliptin | Type 2 diabetes | 1 |
| Sitagliptin | Type 2 diabetes | 3 |
| Sitagliptin/metformin | Type 2 diabetes | 2 |

| | | |
|---|---|---|
| Telmisartan | Hypertension | 3 |
| Telmisartan/hydrochlorothiazide | Hypertension | 1 |
| Trandolapril/verpamil | Hypertension | 3 |
| Vildagliptin | Type 2 diabetes | 1 |

**Table 9 Generic name, indications, and frequency of promoted clinical outcome drugs in France**

| **Generic Name** | **Indication(s)** | **Frequency** |
|---|---|---|
| Amlodipine /perindopril | Hypertension; CAD risk | 11 |
| Atorvastatin | Lipid control; CAD risk | 3 |
| Candesartan | Hypertension; HF | 4 |
| Irbesartan | Hypertension; Renal disease | 3 |
| Nebivolol | Hypertension; HF | 3 |
| Valsartan | Hypertension; Post-MI; HF | 2 |
| Zofenopril | Hypertension; Post-MI | 2 |

**Table 10 Generic name, indications, and frequency of promoted surrogate outcome drugs in the US**

| Generic Name | Indication(s) | Frequency |
|---|---|---|
| Aliskiren | Hypertension | 1 |
| Aliskiren/valsartan | Hypertension | 4 |
| Amlodipine/telmisartan | Hypertension | 1 |
| Exenatide | Glycemic control | 2 |
| Ezetimibe | Lipid control | 1 |
| Ezetimibe/simvastatin | Lipid control | 4 |
| Fenofibrate | Lipid control | 2 |
| Fenofibric acid | Lipid control | 7 |
| Insulin detemir | Types 1 and 2 diabetes | 3 |
| Insulin glargine | Types 1 and 2 diabetes | 5 |
| Insulin glulisine | Types 1 and 2 diabetes | 1 |
| Liraglutide | Type 2 diabetes | 2 |
| Metformin/sitagliptin | Type 2 diabetes | 1 |
| Nebivolol | Hypertension | 15 |
| Niacin/simvastatin | Lipid control | 1 |
| Olmesartan | Hypertension | 1 |
| Pioglitazone | Type 2 diabetes | 3 |
| Pramlintide | Types 1 and 2 diabetes | 1 |
| Rosiglitazone | Type 2 diabetes | 3 |
| Saxagliptin | Type 2 diabetes | 19 |
| Sitagliptin | Type 2 diabetes | 3 |
| Sitagliptin/metformin | Type 2 diabetes | 1 |

**Table 11 Generic name, indications, and frequency of promoted clinical outcome drugs in the US**

| Generic Name | Indication(s) | Frequency |
|---|---|---|
| Atorvastatin | CAD risk | 7 |
| Irbesartan | Hypertension; Renal disease | 1 |
| Losartan | Hypertension; Renal disease | 1 |
| Nicotinic acid | Lipid control; MI risk | 1 |
| Rosuvastatin* | Lipid control; MI & stroke risk | 3 |
| Telmisartan | Hypertension; MI and stroke risk | 3 |
| Valsartan | Hypertension; HF; MI risk | 3 |

*Post-February 2010, reduction of cardiovascular morbidity and mortality was added as indication for rosuvastatin.

## Appendix D - Missing cases

**Table 12 Missing values**

| Variable | Missing values, n (%) |
|---|---|
| Approved drug efficacy | 0 |
| Country | 0 |
| If drug previously prescribed | 0 |
| If drug previously promoted | 0 |
| Group or one-on-one visit | 3 (0.7) |
| Duration of promotion | 0 |
| Frequency of visits received | 5 (1.0) |
| Physician affiliation with medical faculty | 13 (2.9) |
| Number of physicians in practice | 6 (1.3) |
| Physician year of graduation | 0 |
| Total missing values | 27 (>0.1) |

## Appendix E - Variable definition and selection

**Table 13 Variable type and definition**

| Variable | Variable type | Definition |
|---|---|---|
| Approved drug efficacy | Dichotomous | Drug approved by the national regulatory authority either on the basis of 1) surrogate outcomes or 2) serious morbidity or mortality outcomes |
| Country | Categorical | Sales visit took place in 1) Canada, 2) France or 3) US |
| If drug previously prescribed | Dichotomous | The physician, either with or without receiving promotion by a PSR first, had previously prescribed the drug |
| If drug previously promoted | Dichotomous | The same and/or a different PSR had previously promoted the drug to the physician |
| Group or one-on-one visit | Dichotomous | The PSR promoted the drug 1) one-on-one or 2) in a group setting (i.e. in the presence of other healthcare professionals) |
| Duration of visit | Categorical | The promotion lasted: 1) ≤ 5minutes 2) 6-10 minutes, 3) 11-20 minutes or 4) >20 minutes |
| Frequency of visits received | Categorical | The physician receives visits by PSRs: 1) once a month or less 2) once every two weeks 3) once every week or 4) twice or more every week |
| Physician affiliation with medical faculty | Dichotomous | The physician was a preceptor for medical students, interns or residents |
| Number of physicians in practice | Categorical | The physician practiced in an office 1) solo 2) with 2 to 3 other physicians or 3) >3 other physicians |
| Sex of physician | Dichotomous | Male or female physician |
| Physician year of graduation | Continuous | Year of physician's graduation from medical school |
| If industry funding received | Categorical | The physician received funding from industry from one or more of the following sources: 1) study participation 2) advisory boards 3) speakers' bureaus 4) travel expenses 5) unrestricted educational grants or 6) other |
| Number of patients seen per week | Continuous | The number of patients seen by the physician every week |

**Table 14 Variables in GEE model for outcome 1***

| Variable | Included in model? | *p*§ |
|---|---|---|
| Approved drug efficacy | Yes | - |
| Country | No | - |
| If drug previously prescribed | Yes | - |
| If drug previously promoted | Yes | - |
| Group or one-on-one visit | Yes | - |
| Duration of visit | Yes | - |
| Frequency of visits received | Yes | - |
| Physcian affiliation with medical faculty | Yes | - |
| Number of physicians in practice | Yes | - |
| Sex of physician | No | >0.2 |
| Physician year of graduation | Yes | <0.2 |
| If industry funding received | No | >0.2 |
| Number of patients seen per week | No | >0.2 |

*Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs
§Variables forward selected on the basis of a *p* value greater than 0.2: sex of physician, physician year of graduation, industry funding, and number of patients seen per week

**Table 15 Variables in GEE model for outcome 2***

| Variable | Included in model? | *p*§ |
|---|---|---|
| Approved drug efficacy | No | - |
| Country | Yes | - |
| If drug previously prescribed | Yes | - |
| If drug previously promoted | Yes | - |
| Group or one-on-one visit | Yes | - |
| Duration of visit | Yes | - |
| Frequency of visits received | Yes | - |
| Physician affiliation with medical faculty | Yes | - |
| Number of physicians in practice | Yes | - |
| Sex of physician | No | >0.2 |
| Physician year of graduation | Yes | <0.2 |
| If industry funding received | No | >0.2 |
| Number of patients seen per week | No | >0.2 |

*Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate outcome drugs in Canada versus France versus US
§Variables forward selected on the basis of a *p* value greater than 0.2: sex of physician, physician year of graduation, industry funding, and number of patients seen per week

## Appendix F - GEE analysis parameters

### Outcome 1: Frequency of reported claims of serious morbidity or mortality benefit in promotions for surrogate versus clinical outcome drugs

**GEE parameters:**

- Subject variable: physician
- Correlation matrix: exchangeable
- Type of model: binary logistic
- Response (dependent) variable: mention of serious morbidity and/or mortality benefit
- Predictors: approved drug efficacy, if drug previously prescribed, if drug previously promoted, group or one-on-one visit, duration of visit, frequency of visits received, physician affiliation with medical faculty, and number of physicians in practice
- Covariates: physician graduation year

### Outcome 2: Frequency of reported claims of serious mortality or mortality benefit in promotions for surrogate outcome drugs in Canada versus France versus US

**GEE parameters:**

- Subject variable: physician
- Correlation matrix: exchangeable
- Type of model: binary logistic
- Response (dependent) variable: mention of mortality/serious morbidity benefit
- Predictors: country, if drug previously prescribed, if drug previously promoted, group or one-on-one visit, duration of visit, frequency of visits received, physician affiliation with medical faculty, and number of physicians in practice
- Covariates: physician graduation year