USE OF SURROGATE OUTCOMES IN MEDICAL JOURNAL ADVERTISING IN CANADA

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ABSTRACT

Medical journal advertisements make claims for some products based on surrogate outcomes and do not point out that these drugs have not been shown to influence hard clinical outcomes. Some drugs approved on the basis of surrogate outcomes have later had to be withdrawn from the market because of safety problems. Changing the wording in the Product Monograph would require drug manufacturers to note the limits of knowledge about these products.

Key Words: *Health Canada, journal advertisements, Pharmaceutical Advertising Advisory Board, product monograph, surrogate outcomes*

In the case of some medical problems where complications typically take a long time to manifest, for example type II diabetes, hyperlipidemia, hypertension and osteoporosis, Health Canada usually approves New Active Substances (NAS – molecules that have never been marketed before in Canada in any form) for marketing based on surrogate outcome data. Although the percent of products approved by Health Canada on the basis of surrogate endpoints has not been analyzed, from January 1998 through to June 30 2008, the United States (US) Food and Drug Administration (FDA) used surrogate outcomes to approve 69 of 204 (34%) new molecular entities (NME is the American equivalent of NAS) that went through its traditional review process.[1]

The indications for products plus a variety of other information are contained in a Health Canada-approved document, the Product Monograph (PM), that is issued upon approval. Drug companies can only promote their products for indications for which they have been approved. Therefore, when companies run advertisements for these drugs in medical journals they can only use the changes in surrogate outcomes as the basis for the claims they make in their advertisements. One relatively recent example is an advertisement for Onglyza (saxagliptin) that promotes the product for its effectiveness in reducing $HbA1_c$ levels in people with Type II diabetes.

Medical journal advertisements are prescreened by the Pharmaceutical Advertising Advisory Board (PAAB) to ensure compliance with its Code of Advertising Acceptance.[2] The PAAB is a multistakeholder organization with representatives on its board from professional organizations representing doctors, pharmacists, consumers, brand-name and generic manufacturers, advertisers and medical publishers. The brand-name pharmaceutical companies that are members of Rx&D have voluntarily agreed that they will submit all medical journal advertisements for prescription medications for prescreening by the PAAB. According to the PAAB Code as long as printed material from pharmaceutical companies is consistent with the contents of the PM the advertisement is acceptable. Therefore, if the PM lacks a statement indicating that the medication has not been shown to have an effect on a hard clinical endpoint then advertisements do not need to contain a statement to this effect.

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Evidence from the US shows that doctors generally are not aware of the FDA approved indications of routinely prescribed drugs.[3] There is little reason to believe that the results would be different here in Canada. Reading the PM would give doctors a clear picture about approved indications but doctors routinely do not read this document. The latest survey about readership of product monographs shows that only about 1% of a national sample of health care professionals (dentists, naturopaths, pharmacists and physicians) consult the product monograph for safety information.[4] Although this was a survey of four groups of health professionals, the 1% figure means that if it was only doctors and none of the members of the other groups that read the monograph that would translate into fewer than 4% of the 300 doctors surveyed.

When physicians prescribe solely on the basis of surrogate outcomes they may not have a true appreciation of the benefit: harm ratio since randomized controlled trials using this type of outcome typically report larger treatment effects than trials reporting final patient outcomes.[5] There are a number of examples where drugs were approved on the basis of surrogate endpoints and then widely prescribed only to later be removed from the market or have their prescribing significantly restricted because of safety concerns, e.g., cerivastatin (Baycol) for hyperlipidemia that caused fatal cases of rhabdomyolysis, rosiglitazone (Avandia) for type II diabetes that increased the risk of myocardial infarction and flecainide (Tambocor) for cardiac arrhythmias that increased cardiac mortality.[6]

Concerns about the use of unmodified surrogate outcomes in journal ads were raised with the PAAB in 2011 when it was reviewing its Code. PAAB "believe[d] the suggestion [to require a statement about the lack of hard clinical outcomes in ads] may have merit due to international movement to recognize outcomes as more important in clinical decisions than mere surrogate marker measurement."[7] However, the position of the organization was that since its rules about the content of advertisements follow what is in the PM the issue should more properly be discussed with Health Canada through a request for a modification in the contents of the PM. As a result, a letter was sent to Health Canada in early April 2012 requesting that when products are approved using surrogate endpoints the PM include a statement that the medication has not been shown to have an effect on a hard clinical endpoint. (Letter to Health Canada, April 2, 2012) The issue was discussed at a meeting between Health Canada and Canadian advertising preclearance agencies, including PAAB. The position of Health Canada was that "non-indications…will continue to be added, based on an individual assessment" but "lists of non-indications clutter the text of the Product Monograph and may contribute to confusion and be incorrectly recalled later by a prescriber as an actual indication."[7]

An extensive list of non-indications in the PM is not necessary nor is there a need for Health Canada to stop approving drugs based on surrogate outcomes where this is appropriate. Since the PAAB requires that advertisements must be consistent with the PM, if the PM included a statement to the effect "This product was approved on the basis of only surrogate endpoints and not on the grounds that it affects morbidity or mortality," this statement would also have to appear in advertisements. The PAAB could revise its code to ensure that the statement is placed in a prominent position in the ad and not buried in the fine print. This type of statement would alert physicians to the limitations in the knowledge about products and would provide them with additional information to inform their prescribing practices.

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