Postmarket safety of surrogate and clinical outcome drugs approved by Health Canada: a cohort study

Joel Lexchin MSc, MD

Professor, School of Health Policy and Management

York University

and

Emergency Physician

University Health Network

and

Associate Professor

Department of Family and Community Medicine

University of Toronto

Toronto, Ontario

Correspondence:

Joel Lexchin MD

School of Health Policy and Management

York University

4700 Keele St.

Toronto, ON M3J 1P3

Tel: 416-736-2100 x 22119

Fax: 416-736-5227

E mail: jlexchin@yorku.ca

Abstract

Background

Health Canada approves drugs on the basis of clinical and surrogate outcomes. This study compares the postmarket safety of these two groups.

Methods

Information about whether surrogate or clinical outcomes were used and the date of market approval came from the Summary Basis of Decision. Safety warnings and the dates they were issued were identified through advisories on the MedEffect Canada web site. The percent of surrogate and clinical outcome drugs with a serious safety warning was compared. Kaplan-Meier survival curves were calculated to determine the likelihood that drugs in each group would receive a serious safety warning. The time from market authorization until a first safety warning was compared for the two groups of drugs.

Results

128 drugs were approved using clinical outcomes compared to 110 with surrogate outcomes. 19.5% of clinical outcome drugs (25/128) had a serious safety warning compared to 15.5% (17/110) for surrogate outcome drugs ($p = 0.4958$). There was no difference in Kaplan-Meier curves for the two groups ($p = 0.3642$). The median time between market authorization and a warning for clinical outcome drugs was 661 days versus 946 days for surrogate outcome days ($p = 0.5892$).

Interpretation

On all three metrics used there is no difference in the postmarket safety of surrogate and clinical outcome drugs. At the same time, when surrogate outcome drugs are approved

their benefit:harm ratio is not fully established. Health Canada should require clinical outcome postmarket trials for surrogate outcome drugs as a condition of approval.

Introduction

Health Canada approves drugs on the basis of clinical trials that use clinical outcomes, surrogate outcomes or a combination of both, where clinical outcomes are those that have direct relevance to patients such as a change in symptoms, morbidity or mortality. The United States Institute of Medicine defines surrogate outcomes as ""biomarker[s] intended to substitute for a clinical endpoint [and] expected to predict clinical benefit (or harm . . .) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence" (1). The use of surrogate outcomes is attractive to many groups involved with pharmaceuticals including industry, regulators, health care practitioners and patients. They allow trials to be done less expensively with fewer patients and more quickly and therefore promising new drugs can reach patients faster. However, for surrogate outcomes to be reliable predictors of clinical outcomes they must be a correlate of the true clinical outcome and fully capture the net effect of treatment on the clinical outcome (2). Surrogate outcomes can fail to accurately predict clinical effects for various reasons, the most important being that the intervention that affects a surrogate endpoint might affect the true clinical outcome by unintended mechanisms of action that are independent of the disease process. Therefore, the effects of the intervention could be substantially offset by unintended, unanticipated, or unrecognized mechanisms (3).

Past history and recent events show that some drugs approved on the basis of surrogate outcomes can ultimately have serious safety problems and need to be withdrawn from the market or have their indications significantly restricted (4). Encainide and flecainide were both approved based on their ability to suppress cardiac arrhythmias after a myocardial

infarction but when tested in a randomized clinical trial caused more cardiac deaths than placebo (5). Dexfenfluramine and fenfluramine were approved on the basis of short-term trials showing that they reduced weight but ultimately their relationship to cardiac valvulopathy caused them to be withdrawn from the market (6). More recently, although rosiglitazone lowered hemoglobin HbA1c, a meta-analysis found that it was associated with an increase in myocardial infarctions (7). Even if one class of drugs demonstrates an overall clinical benefit (benefits outweigh harms) that does not necessarily imply that another class that produces the same surrogate outcome will also show the same net clinical benefit. Both alpha blockers and thiazides lower blood pressure but compared to doxazosin, chlorthalidone had an equal risk of coronary heart disease death and nonfatal myocardial infarction but significantly reduced the risk of combined cardiovascular disease events (8).

Since at the time of approval the ultimate benefit of many drugs approved using surrogate outcomes is much less certain than that of drugs that use clinical outcomes, it is important to compare their postmarket safety. If surrogate outcome drugs are less safe than those approved on the basis of clinical outcomes and possibly less beneficial, then their overall benefit:harm ratio will be less favourable and these drugs should be used with significant caution. This study compares the postmarket safety of drugs approved on the basis of surrogate outcomes with those approved on the basis of clinical outcomes. Specifically it asks whether there is a difference in the percent of each group of drugs where a serious safety issue is identified, the likelihood that Health Canada will issue a serious safety warning for the former group compared to the latter group and how long it takes for a

serious safety issue to be recognized in each group. Secondarily, this study examines the time spent in the review process and the type of review that the different groups underwent. Health Canada utilizes three different approval mechanisms – standard, priority and Notice of Compliance with conditions (NOC/c – approval conditional on the company completing additional clinical studies), with different timelines – 300, 180 and 200 days respectively (9). Since one of the rationales for using surrogate outcomes is to get promising new drugs to patients more quickly they may also be more likely to undergo a quicker review. Drugs that are approved with either a priority review or a NOC/c are more likely to acquire a serious safety warning than drugs with a standard review (10, 11).

Methods

Since January 1, 2005, after Health Canada approves a new drug it issues a document, the Summary Basis of Decision (SBD, available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/index-eng.php), that outlines the clinical grounds used to grant market authorization. All SBDs issued until December 31, 2014 were read to determine if the clinical trials for the product used surrogate or clinical outcomes. Clinical outcomes were defined as changes in symptoms, quality of life, morbidity, mortality or any other outcome that reflected "how a patient feels, functions or survives" (12). Surrogate outcomes were defined as "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy" (12). SBDs issued in Phase 1 contained information about

outcomes in two places, Sections 2 and 3.3.4. SBDs issued in Phase II (starting on June 29, 2012) had the same information in Sections 2 and 7. In addition to the type of outcomes used, the following additional information was extracted from the SBD: generic name, brand name, company marketing the product, therapeutic indication, date of new drug submission (application to market the drug) and date of notice of compliance (date of marketing authorization). Only the outcomes defined as primary objectives in pivotal trials were used. Health Canada defines pivotal trials "as trials of high scientific quality, which provide the basic evidence to determine the efficacy, properties, and conditions of use of the drug" (13). If a drug was approved for one or more indication(s) using both clinical and surrogate outcomes then it was deemed to be approved based on a clinical outcome.

Information about the approval process – standard, priority and NOC/c - came from the annual reports of the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate available by directly contacting the directorates at <publications@hc-sc.gc.ca>. For drugs approved after April 1 2013 these reports were supplemented by information on the Notice of Compliance web site (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp).

Safety warnings and drug withdrawals for the period January 1, 2005 to December 31, 2014 were identified through advisories for health professionals on the MedEffect Canada web site <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>. For each safety advisory or notice of withdrawal of a product, the date was

recorded. All serious safety advisories (those using bold black print and/or boxed warnings) were included except for those dealing with the withdrawal of a specific batch or lot number due to manufacturing problems or those issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one). If a drug received more than one serious safety warning only the time to the first warning was used. When necessary, notices on the MedEffect web site were supplemented by searching on the product name in the Drug Product Database (DPD) <http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>. The DPD contains product specific information on drugs approved for use in Canada as well as all products discontinued since 1996.

The percent of clinical outcome drugs with either a serious safety warning or that were withdrawn because of safety issues was compared to the percent of surrogate outcome drugs with a Chi square test. Kaplan-Meier survival curves were calculated for the period from market authorization receipt until a first safety warning or withdrawal for drugs with surrogate and clinical outcomes and curves were compared using a Log rank (Mantel-Cox) test. A Kaplan-Meier analysis accounts for the fact that some drugs had received a safety warning and some had not by the end of the study period (December 31, 2014).

The time between application for market authorization and receipt of approval and the time between receipt of approval and a safety warning and/or withdrawal from the market were calculated in days. Means are reported for the first time period and compared using

a t-test and medians are reported for the second as these values are not normally distributed (Shapiro-Wilk test) and were compared using the Mann-Whitney test. The percent of surrogate outcome drugs that were approved under the three different approval processes was compared to the percent of clinical outcome drugs approved under the three processes, using a Chi square test. Counts were made of the number of clinical and surrogate outcome drugs approved for different therapeutic uses. Values of $p < 0.05$ were considered significant. Calculations were done using Excel 2011 for Macintosh (Microsoft) and Prism 6.0 (GraphPad Software).

Results

There were a total of 251 drugs with SBD documents. Thirteen drugs were eliminated: 5 were diagnostic agents, 5 were either bioequivalents or subsequent entry biosimilars and there were no outcomes documented, 2 were vaccines approved on an emergency basis and 1 product, a disinfectant, was not used for treating humans. Out of the remaining 238 drugs, 128 used clinical outcomes and 110 used surrogate outcomes.

Twenty-five clinical outcome drugs (19.5%, 95% CI 13.6, 27.2) either had a serious safety warning or were withdrawn (22 serious safety warning only, 4 withdrawn 1 with a previous warning) compared to 17 surrogate outcome drugs (15.5%, 95% CI 9.9, 23.4) (16 serious safety warning only, 1 withdrawn with a previous warning) ($p = 0.4958$). There was no difference in Kaplan-Meier curves for the two groups of drugs (Figure 1, $p = 0.3642$), meaning that the likelihood of drugs in each group acquiring a serious safety warning after they were marketed was the same. The median time for a warning for

clinical outcome drugs was 661 days (interquartile range 506, 1254) versus 946 days (interquartile range 556, 1566) for surrogate outcome days (p = 0.5892).

Clinical outcome drugs spent a mean of 452 days in the review process (95% CI 409, 496) compared to 474 days (95% CI 422, 527) for surrogate outcome drugs (p = 0.5155). 102 clinical outcome drugs underwent a standard approval, 24 a priority approval and 2 were approved with a NOC/c. Comparable figures for surrogate outcome drugs were 66, 27 and 17, respectively (Table 1, p < 0.0001).

Table 1 shows the distribution of therapeutic indications for clinical and surrogate outcome drugs. Drugs for allergy, dermatology, genitourinary, gastrointestinal, "other" infectious diseases, neurology, psychiatry and rheumatology were much more likely to use clinical outcomes whereas drugs for cancer, diabetes, hepatitis, HIV and "other" metabolic diseases were much more likely to use surrogate outcomes. 31% (12 out of 39) of cancer drugs with surrogate outcomes were approved under the NOC/c process whereas none of the 13 cancer drugs with clinical outcomes used this approval process.

Interpretation

On all of the measures of safety consider in this study – percent of drugs acquiring a serious safety warning or being withdrawn from the market, likelihood that Health Canada will issue a serious safety warning and time from market approval to first serious safety warning – surrogate outcome drugs were no different from clinical outcome drugs. In view of the anecdotal evidence about safety issues with some surrogate outcome drugs

this is reassuring news. The comparable postmarket safety profiles of these two groups of drugs may also be a reflection of the finding that clinical and surrogate outcomes drugs spent an equal amount of time in the review process.

At the same time, we need to recognize that the metrics used here are only indirect measures of safety; they do not measure the number of people potentially affected by safety problems nor the seriousness of the harms that the drugs cause. Additionally, the information about safety from this study does not tell us whether the benefit:harm ratio for the two groups of drugs is equivalent. A recent meta-analysis found that clinical trials that used surrogate outcomes were more likely to report larger treatment effects than trials reporting final clinical outcomes, a conclusion that could not be explained by differences in the risk of bias or characteristics of the two groups of trials (14). This finding suggests that the benefit:harm ratio for clinical outcome drugs may be more robust than that of surrogate outcome drugs.

The difference between surrogate and clinical outcome drugs in the review processes that they undergo is indirectly a reflection of wanting to get some surrogate outcome drugs to the market more rapidly as the difference in the types of reviews reflects the fact that drugs for some high priority indications are much more likely to use surrogate outcomes. 75% (39/52) of cancer drugs had surrogate outcomes and twelve of these 39 went through the NOC/c approval process. Similarly, 8 of 9 drugs for HIV used surrogate outcomes and 2 of the 8 were approved with a NOC/c.

Whether surrogate outcomes should continue to be widely used for drugs for some therapeutic indications is open to question. Cancer drugs are frequently approved on this basis in multiple jurisdictions. Garattini and Bertele (15) looked at 12 oncology drugs approved by the European Medicines Agency (EMA) from 1995 to 2000. The end points for the clinical trials for these drugs tended to be subjective such as "time to progression" and there was seldom an evaluation of survival or quality of life. A second study examined 14 cancer drugs approved by the EMA for 27 indications from January 1995 to December 2004. Only 2 of those 27 were supported by changes in overall survival compared to 13 for response rate, 11 for time to progression or progression-free survival and 1 for "other" (16). Tumour size does not correlate with overall survival(17) and the utility of progression free survival as a valid biomarker seems to depend on the type of cancer being treated (17-19). The continued use of surrogate outcomes as the basis for approval of drugs to treat non-insulin dependent diabetes seems difficult to justify (20) but all 9 drugs approved for this indication used surrogate outcomes.

The major limitation to this study is that all of the surrogate outcomes were treated equally and not assessed for their validity. This would be difficult to accomplish in many cases as the example of disease free progression in cancer illustrates, where it seems to be valid for some cancers and not for others. Using an increase in CD4 cell count in HIV as a surrogate for improved survival can present difficulties in interpretation. A 1993 review looked at 16 trials of drug therapy for HIV that used the CD4 cell count as a surrogate endpoint (21). An increase in cell count was significantly favourable in 7 of the 8 trials in which treatment improved the clinical outcome of progression to AIDS or death. But at

the same time there was also an increase in CD4 cell count in 6 out of 8 trials in which treatment did not improve progression to AIDS or death (3).

Surrogate outcomes are reasonable in rare circumstances such as amyotrophic lateral sclerosis that are uniformly but slowly fatal and lack effective therapy, in the case of very rare diseases where validation of hard end points may take an unreasonable time to complete or where it is ethically impossible to test candidate drugs such as exposure to biological or chemical weapons (4). Based on the metrics used in this study, surrogate outcome drugs are just as safe as clinical outcome ones, but at the time of approval their benefit:harm ratio is not as clear because of the lack of definitive evidence about their benefits. Therefore, in the vast majority of cases where surrogate outcomes are used, Health Canada should take advantage of the new powers vested in it through Bill C-17 (22) and require companies to initiate postmarket trials with clinical outcomes as a condition of approval. The outcome of these trials will more definitively establish the benefit:harm ratio so that these drugs can be used in the most appropriate manner.

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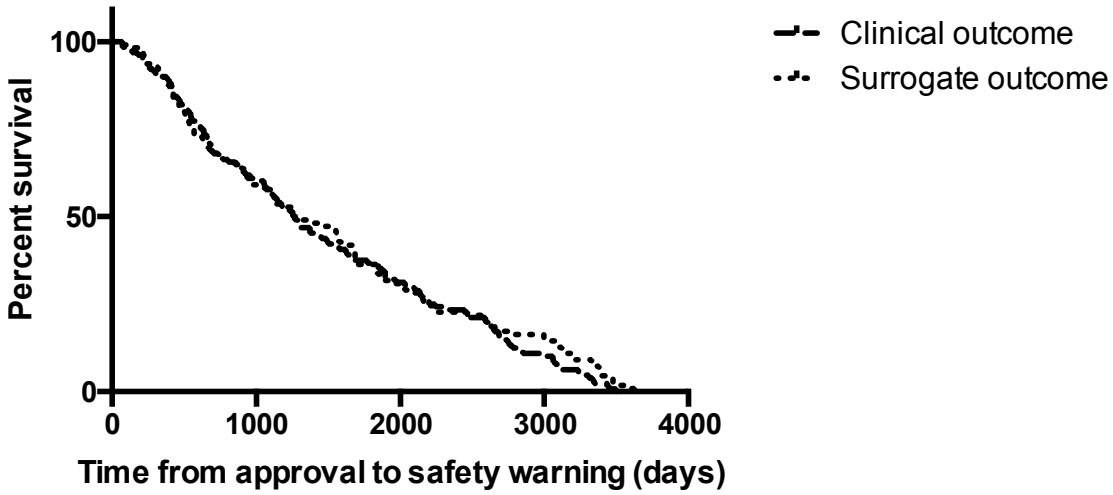
Table 1: Disease area, outcome used and approval type

Disease area	Outcome used for approval					
	Clinical			Surrogate		
	Standard	Priority	NOC/c*	Standard	Priority	NOC/c*
Allergy	3	0	0	0	0	0
Cancer	4	9	0	18	9	12
Cardiovascular	2	2	0	5	0	1
Dermatology	6	0	0	0	0	0
Genitourinary	6	0	0	0	0	0
Gastrointestinal	7	1	0	0	0	0
Gynecology	2	0	0	1	0	0
Hematology	6	1	0	3	1	1
Inborn error of metabolism	1	2	0	2	1	0
Infectious disease, hepatitis	0	0	0	0	6	0
Infectious disease, HIV	0	0	1	4	2	2
Infectious disease, other	12	2	1	0	0	0
Infectious disease, vaccine	3	2	0	6	1	0
Metabolic disease, diabetes	0	0	0	9	0	0
Metabolic disease, other	1	0	0	9	3	0
Miscellaneous	6	1	0	0	0	1
Musculoskeletal	3	0	0	0	0	0
Neurology	16	1	0	1	0	0
Ophthalmology	3	2	0	1	1	0
Psychiatry	13	0	0	0	0	0
Pulmonary hypertension	1	0	0	2	2	0

Respirology	2	0	0	5	1	0
Rheumatology	5	1	0	0	0	0
Total	**102**	**24**	**2**	**66**	**27**	**17**

*NOC/c = Notice of Compliance with conditions

Figure 1: Kaplan-Meier curve showing time to first serious safety warning or removal from market for drugs approved with clinical and surrogate outcomes



No significant difference between curves, p = 0.3642, Log rank (Mantel-Cox) test