Journal of Diabetes Science and Technology
Volume 7, Issue 2, March 2013

SYMPOSIUM

An Overview of Canadian and U.S. Approaches to Drug Regulation and Responses to Postmarket Adverse Drug Reactions

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Abstract

Over the years, drug products, including those indicated for diabetes, have been withdrawn from the marketplace because of quality concerns and/or severe adverse drug reactions. While the drug regulatory process is designed to detect, among other things, adverse drug reactions before a drug receives marketing authorization, for various reasons, premarket detection of all potential adverse reactions associated with a drug may not be possible. As such, regulatory authorities must also react to and manage adverse reactions identified at the postmarket stage. In this article, we provide a general overview of drug regulation in Canada and the United States and consider an example of a drug indicated for the treatment of diabetes and how newly identified potential safety concerns were managed in the postmarket environment.

J Diabetes Sci Technol 2013;7(2):313–320

Introduction

The current scheme for regulating pharmaceuticals in Canada has been in place, substantially unchanged, since the 1960s.[1] The current version of the legislative regime is set out in the Food and Drugs Act[2] (the "Act") and the Food and Drug Regulations[3] (the "Regulations") made thereunder. Health Canada is tasked with applying the Act and the Regulations to ensure that pharmaceutical products sold in Canada are safe, effective, and properly labeled.[4] In order to assist drug manufacturers in complying with the statutory framework, Health Canada publishes guidance documents and policies that interpret the Act and the Regulations. While these guidance documents and policies do not have the force of law, they are an invaluable tool for manufacturers, because they expound how Health Canada will apply the Act and the Regulations.

Part of Health Canada's mandate is to regulate the pre- and postmarket stages of the drug marketing authorization process. A key component of postmarket regulation requires Health Canada to monitor and react to reports of adverse drug reactions. As such, the scope of Health Canada's postmarket oversight responsibilities has direct and significant implications for pharmaceutical manufacturers and consumers.

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Abbreviations: (DIN) drug identification number, (FDA) Food and Drug Administration, (FFDCA) Federal Food, Drug, and Cosmetic Act, (GSK) GlaxoSmithKline Inc., (IND) investigational new drug, (NDA) new drug application, (NOC) notice of compliance, (NOC/c) NOC with conditions, (NOC/c-QN) NOC with conditions qualifying notice, (PMC) postmarket commitment, (PMR) postmarketing requirement, (REMS) risk evaluation and mitigation strategy, (U.S.) United States

Keywords: adverse drug reaction, postmarket surveillance

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In contrast to the Canadian regime, the regulatory system in the United States (U.S.) has undergone a number of statutory amendments to strengthen postmarket regulatory oversight.

This article describes the regulatory tools currently available to Health Canada, the tools available to the Food and Drug Administration (FDA) in the United States and contrasts them with those available to Health Canada using the diabetes drug, AVANDIA, as an example.

Drug Regulation in Canada

Overview

Before any drug can be sold on the Canadian market for human use, the manufacturer (or sponsor) must present substantive scientific evidence of the drug's safety, efficacy, and quality. If clinical trials are to be conducted in Canada, manufacturers must submit a clinical trial application to Health Canada and receive authorization to perform most developmental stage drug trials, clinical trials involving marketed drugs where the proposed trial is outside of the parameters of the marketing authorization for the drug, and clinical trials with products that have received conditional marketing authorization.[5] If a sponsor is able to furnish sufficient evidence and fulfills all regulatory requirements, Health Canada will grant the sponsor a Notice of Compliance (NOC) and assign a drug identification number (DIN). Once a drug has received a NOC and DIN, the sponsor is authorized to sell the product on the Canadian market.

If, however, the sponsor is unable to furnish sufficient evidence of safety and efficacy, Health Canada may issue a Notice of Noncompliance and request that the sponsor submit additional evidence.[6]

Alternatively, Health Canada may issue the sponsor a NOC with Conditions (NOC/c) when there is a need to provide access to promising new drugs for patients suffering from serious, life-threatening, or severely debilitating diseases or conditions for which no drug is presently marketed in Canada. A NOC/c may also be issued when a significant increase in efficacy or a significant decrease in risk is demonstrated in relation to an existing drug marketed in Canada.[7]

If evidence submitted qualifies under the NOC/c policy, Health Canada may issue a NOC/c Qualifying Notice (NOC/c-QN), which indicates that the drug submission qualifies for a NOC under the NOC/c policy and which outlines any additional clinical evidence to be provided in confirmatory trials, postmarket surveillance responsibilities, and any advertising, labeling, or distribution requirements. Within 30 days of receiving the NOC/c-QN, the manufacturer must provide a response to Health Canada, including, where applicable, an initial outline of proposed confirmatory trials. If Health Canada is satisfied with the manufacturer's response to the NOC/c-QN, it will issue a NOC/c, which requires, among other things, that the manufacturer carry through with any confirmatory trials and comply with postmarket surveillance requirements.[7]

Postmarket Surveillance in Canada

Under the Act and the Regulations, drug manufacturers have an ongoing legal obligation to monitor the safety and efficacy of their drug products following market entry. Sections C.01.016 to C.01.019 of the Regulations prohibit a manufacturer from selling a drug unless the manufacturer submits to Health Canada within 15 days all information related to any serious adverse drug reaction that has occurred in Canada and any serious unexpected adverse drug reaction that has occurred outside of Canada with respect to the drug. A serious adverse drug reaction is "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."[8]

The Regulations also require manufacturers to prepare an annual summary report of all information relating to both adverse drug reactions and serious adverse drug reactions to determine whether there has been a significant change in the risks and benefits of a drug.[9] An adverse drug reaction is "a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of

an organic function."[8] If a significant change in the risks and benefits of the drug is identified, the Minister of Health may request that the manufacturer submit annual summary reports and/or case reports related to the known adverse drug reactions.[10]

The Marketed Health Products Directorate of Health Canada is responsible for, among other things, monitoring and collecting data on adverse reactions. In addition to manufacturer reporting, Health Canada may also gather adverse reaction data from health care professionals, the public, registries and databases maintained in or by other jurisdictions and groups/organizations, clinical and/or epidemiological studies, communications from foreign regulators, and scientific literature.[11] The Marketed Health Products Directorate also reviews marketed health product safety data, conducts risk/benefit assessments of marketed health products, and coordinates with manufacturers to communicate product-related risks to both health care professionals and the public.[12]

Health Canada acknowledges that it has no authority under the Act or the Regulations to compel a manufacturer to disseminate communications to health professionals ("health professional communications") or to the public ("public communications").[13] These communications are usually issued by manufacturers voluntarily or at the request of Health Canada. If, however, a manufacturer refuses to cooperate with a request, Health Canada may choose to post a warning or advisory to the departmental Web site, disseminate the health professional communication or public communication itself, or cancel the marketing authorization of a drug product under section C.01.013 of the Regulations.[13]

In addition to adverse reaction monitoring, Health Canada is also involved at the postmarket stage through the use of postmarket commitments (PMCs). Health Canada may use PMCs, for example, to ensure that industry sponsors that have been granted a NOC/c commit to conducting postmarket trials to establish substantial evidence of safety and efficacy. In this way, PMCs are used to complete the data set for NOC/c authorizations.[14] If a manufacturer does not complete its PMCs, Health Canada may work with the manufacturer to facilitate completion of the conditions set out therein. If, for some reason, the manufacturer is unable to comply with its PMCs, Health Canada may exercise its enforcement powers to remove the drug product from the market. Importantly, Health Canada cannot remove a drug from the market solely on the basis of noncompliance with a PMC; it may only remove a product if there is concern about the safety of the drug.[15,16] Under Section C.08.006(2) of the Regulations, Health Canada may, for a definite or indefinite period, suspend a NOC issued to a manufacturer in respect of a drug product for various reasons, including safety concerns revealed by clinical experience not available at the time of the submission, new information regarding the effect of the drug, and failure to maintain records.[2]

Drug Regulation in the United States

Overview

At a very high level, the drug approval process in the United States can be characterized as similar to that of Canada. The process is regulated by the FDA under the Federal Food, Drug, and Cosmetic Act (FFDCA),[17] and like Health Canada, the FDA issues guidance documents and policies to assist manufacturers in complying with statutory requirements. The approval process begins with the preclinical phase, usually followed by the submission of an investigational new drug (IND) application to the FDA.[18] An approved IND application allows investigators to transport and distribute unapproved drugs across state lines for use in clinical trials.[19] Upon completion of the clinical trials, drug manufacturers may file a new drug application (NDA) with the FDA, which might be approved or rejected or sent back to the sponsor with a request for additional information.[18]

A treatment IND application may be submitted with respect to unapproved drugs showing promise in clinical investigations for serious or immediately life-threatening conditions in patients for whom no comparable or satisfactory alternative drug or other therapy is available.[20,21] Treatment use of an investigational drug is conditional on the sponsor and investigators complying with the safeguards of the IND process, including, among other requirements, the submission of IND safety reports, which require the sponsor to report to the FDA any suspected adverse reaction that is both serious and unexpected; the sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.[20] The sponsor must also

submit safety information from the clinical study to the FDA as prescribed by the postmarketing safety reporting requirements described here.[20]

Postmarket Surveillance in the United States

According to some commentators, the FDA has historically focused its resources on front-end market approval cost–benefit analysis at the expense of postapproval monitoring of drug products.[22] More recently, however, the FDA appears to have adopted a more balanced approach, now spending as much effort and as many resources on postmarket surveillance of drug products as it does in the preapproval process.[22]

Under the postmarketing requirement (PMR) and commitment provisions of the FFDCA,[17,23] drug sponsors may either agree or be required to conduct studies and clinical trials following market approval in order to gather additional information about a product's safety, efficacy, and/or optimal use.[24]

The FDA defines PMCs as studies or clinical trials that a sponsor has agreed to conduct but that are *not required* by statute or regulation.[24] Section 506(B) of the FFDCA requires a drug sponsor that has entered into an agreement with the secretary of Health and Human Services to conduct a postmarketing study of a drug to submit an annual report of the progress of the study or the reasons for the failure of the sponsor to conduct the study.[25]

Postmarketing requirements, on the other hand, are studies or clinical trials that drug sponsors are *required* to conduct under one or more statutes or regulations.[24] Under Section 505(o) of the FFDCA,[26] PMRs may be used to assess a known serious risk related to the use of a prescription drug, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicates the potential for serious risk.[26]

In addition to the use of U.S. PMCs, the FDA Amendments Act of 2007 introduced a risk evaluation and mitigation strategy (REMS) program into the FFDCA.[27] Under Section 505-1, the FDA can require manufacturers to submit a REMS with, among other applications, NDAs and abbreviated NDAs.[28] The FDA may also require a marketing authorization holder to submit a proposed REMS if the FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks.[29]

A REMS must include a timetable for the submission of assessments of the REMS and may also include a medication guide, a patient package insert, and a communication plan to health care professionals. In addition, Section 505-1(f) of the FFDCA lists "elements to assure safe use" that may be required as part of a REMS when the drug product has been shown to be effective but is associated with a serious adverse event and can be approved only if, or would be withdrawn unless, such elements are required as part of such strategy to mitigate a specific serious risk listed in the labeling of the drug.[30] "Elements to assure safe use may require that (a) health care professionals who prescribe the drug have particular training, experience, or certification; (b) health care settings that dispense the drug are specially certified; (c) the drug be dispensed to patients only in certain health care settings, such as hospitals; (d) the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results; (e) each patient using the drug be subject to certain monitoring; and/or (f) each patient using the drug be enrolled in a registry.[30]

Importantly, the FDA has the authority to enforce compliance with PMRs and REMSs by imposing charges under Section 505 of the FFDCA,[31] misbranding charges,[32] and civil monetary penalties.[33]

Rosiglitazone as an Example

AVANDIA (rosiglitazone maleate), an oral antidiabetic agent used in the management of type 2 diabetes marketed by GlaxoSmithKline Inc. (GSK), first received marketing authorization in Canada on March 21, 2000,[34] and in the United States on May 25, 1999.[35] Following market approval, at least one study[36] reported on possible cardiovascular safety issues associated with rosiglitazone use, which prompted responses from both Health Canada and the FDA.

Canada

In 2007, GSK, in conjunction with Health Canada, released communications to health care professionals and the public to address concerns raised about the increased risk of cardiac adverse effects related to the use of rosiglitazone-containing products and to indicate that further investigation was underway.[37,38]

In late 2007, the Scientific Advisory Committee on Metabolic and Endocrine Therapies, struck by the Therapeutic Products Directorate of Health Canada, met, in part, to discuss postmarket cardiovascular safety issues associated with AVANDIA. The committee was tasked with ensuring that planned labeling changes to AVANDIA were adequate to manage current safety concerns. GlaxoSmithKline Inc. attended a portion of the meeting to present data on clinical outcomes, safety issues, and risks of cardio-adverse events. The committee ultimately supported the label changes but indicated that the risk data on rosiglitazone from trials and the literature review were inconclusive on certain safety issues. In supporting the label changes, the committee favored the precautionary approach to labeling also adopted by the FDA in the United States. The committee identified the need for additional trials that would provide more safety and efficacy data.[39]

In consultation with Health Canada, GSK advised the public and health care professionals of new restrictions for the use of rosiglitazone-containing products in patients with type 2 diabetes (e.g., use in combination with other antidiabetic medications) based on Health Canada's review of the information available on cardiovascular safety.[40,41]

In 2010, based on Health Canada's assessment of additional study data, the manufacturer issued further usage restrictions on rosiglitazone-containing products and updated the consumer and prescriber sections of the Canadian product monographs for the products accordingly. One of the added usage restrictions was a recommendation that physicians obtain written informed consent from patients prior to prescribing the drug.[42,43]

In Canada, therefore, the issue of potential cardiovascular risks arising from the use of rosiglitazone-containing products has been jointly managed by the manufacturer and Health Canada through the release of public notices, use restrictions set out in the product monographs, and patient written informed consent. This joint approach has allowed patients requiring the drug to continue to benefit from its use, as it remains within physicians' scope of practice to determine the appropriate circumstances in which rosiglitazone-containing products are prescribed. In this way, the ongoing use of rosiglitazone-containing products is controlled through the physician–patient relationship, taking into consideration information provided by Health Canada and the manufacturer.

United States

Based on clinical studies of rosiglitazone that became available following market approval of rosiglitazone-containing products, the FDA issued an alert to the public and health care professionals to advise of a potential safety issue with rosiglitazone-containing products and adverse cardiovascular effects.[44] In order to address these concerns, the manufacturer of the drugs added new information to the existing boxed warnings.[45]

In 2010, after further consideration of the clinical data, the FDA announced that it would limit the approved uses of AVANDIA and also require GSK to develop a REMS.[46] In early 2011, the FDA approved safety-related changes to physician labeling and medication guides for rosiglitazone-containing products.[47]

The REMS, approved by the FDA in late 2011, required the manufacturer to ensure that (i) health care professionals who prescribe rosiglitazone-containing medications are specially certified, (ii) rosiglitazone will only be dispensed by specially certified pharmacies, and (iii) rosiglitazone will only be used by patients enrolled in the REMS program.[48] Notably, rosiglitazone-containing products are only available to patients enrolled in the Avandia-Rosiglitazone Medicines Access Program by mail order from certified pharmacies participating in the program. Program enrollment requires physicians to attest to and document their patients' eligibility. Additionally, patients are required to review statements describing the cardiovascular safety concerns associated with the drug and acknowledge that they understand the risks.[48]

Unlike the approach taken in Canada, the U.S. approach has been managed by the FDA at the manufacturer level (i.e., the FDA issued safety alerts, requirement of a REMS). In other words, it was within the regulatory authority of the FDA to require the manufacturer to take steps to manage the identified safety concerns at each level of the manufacturer-to-patient distribution chain while still allowing patients requiring the drug to continue to benefit from its use.

Initiatives and Future Directions for Postmarket Regulation in Canada

Health Canada has taken steps to increase its postmarket monitoring activities. These initiatives include establishing formal working groups to consider potential drug safety issues, ensuring that companies comply with adverse drug reaction reporting requirements through the implementation of an inspection program, and reviewing risk management plans that are submitted voluntarily by drug manufacturers.[49]

Additionally, Health Canada has proposed substantial revisions to its drug regulatory scheme as part of a progressive licensing model. Of particular interest are Health Canada's proposals regarding postmarket studies and the use of risk management plans. Health Canada is examining the possibility of requiring marketing authorization holders to submit data from postmarket clinical or epidemiological studies and to conduct studies aimed at a specific safety or efficacy concern.[50,51] These requirements could take the form of blanket conditions applicable to all marketing authorizations or could only attach to certain categories of high-risk products.[50]

The risk management plans, similar to the REMS in the United States, could apply to drugs that have either unknown or increased risks associated with their use, drugs not previously marketed in Canada, and any drug on the Canadian market for which a safety concern has been identified.[52]

In an attempt to enforce compliance with Canada's regulatory regime, Health Canada has also proposed a modernization of the current fines and penalties framework,[53] which may include suspending or refusing to issue drug establishment licenses.[54]

With respect to diabetes therapies specifically, Health Canada issued a notice regarding an interim approach for evaluating cardiovascular risk for new antidiabetic therapies to treat type 2 diabetes. This notice was issued in response to requests for guidance from the pharmaceutical industry regarding data requirements for cardiovascular risk assessments. The notice states that the U.S. approach to filing drug submissions with the FDA for such therapies is an acceptable approach for filing new drug submissions to Health Canada for those therapies. In particular, the notice suggests that, in order to establish the safety of a new antidiabetic therapy to treat type 2 diabetes, the development program for the therapy should include an appropriate analysis of cardiovascular end points. The results of the analysis will determine whether or not Health Canada is likely to require a postmarketing cardiovascular safety trial to be conducted.[55]

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