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Rational Approaches to the Regulation of Nonprescription Medicines

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RATIONAL APPROACHES TO THE REGULATION OF NONPRESCRIPTION
MEDICINES
BY
ANAND S. ACHANTA

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR DEGREE OF DOCTOR OF PHILOSOPHY
IN
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2002

DOCTORAL DISSERTATION

OF

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2002

ABSTRACT

In recent years, self-medication products have undergone a dramatic change due to the advent of herbal medicines, dietary supplements, nutraceuticals and health foods in addition to traditional nonprescription medicines and the increasing societal preferences towards greater individual control over the use of medicines. Globally, the role and importance of nonprescription medicines in healthcare delivery is also rapidly increasing due to the potential cost-savings. Hence, this area is beginning to receive much attention from regulatory authorities, academia and professional/industry/trade organizations.

This dissertation presents a comprehensive analysis of the classification of nonprescription medicines and Rx-to-OTC switch criteria/policy in the United States, United Kingdom, Canada, Japan and Australia. A new approach to investigating US FDA's overall switch regulatory policies through the combined application of case-history evaluations, electronic survey questionnaire and telephone interviews has been utilized.

This investigation was conducted in three phases. Phase-1 involved information retrieval and a critical review of existing literature, phase-2 applied switch case history analyses pertinent to US FDA and phase-3 measured the attitudes/opinions of the academic/professional community and key opinion leaders in nonprescription medicines across the US, Canada, UK and Australia on important questions.

The subject matter of this dissertation is of enormous current interest in the global nonprescription medicines arena. The significance of the results presented in this

dissertation is amplified as this area has received little academic attention and this is perhaps the first comprehensive treatment of this subject.

Overall, inferences based on the information elicited have been summarized to provide data-based responses to questions of global interest in the self-medication arena. This information is especially valuable to the US FDA as they are currently seeking public comment. Data shows that the OTC regulatory model in the United States may be improved. Evidence indicates that principles upon which approaches for improvement of the US regulatory system must be based should include: an objective evaluation of pharmacist class of OTC medicines, development of effective consumer education tools, increase in regulation of non-traditional OTC medicines, acknowledge that not all disease conditions and drug classes are suitable for self-treatment, a collaborative approach by FDA towards switching that includes all stakeholders is more favored, decisions on switch petitions must be case-specific without a presumptive bias and public health benefit must be the paramount evaluation criterion.

ACKNOWLEDGMENTS

The completion of this dissertation in its final form marks the culmination of a long personal journey that has been enriching and enlightening in so many ways that I cannot even describe. Although this is a personal accomplishment, I could not have done it alone without the support and guidance of many generous individuals. I am most grateful to all of them.

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It is not possible to list here all my friends to whom I am very grateful. I thank Swami Iyer, Bina & Bali Gangadharan, Surabhi & Sudhan Marathe, Ravi Pappu and Kathy Hayes who have been very helpful to me in numerous ways.

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TO MY BELOVED PARENTS
FOR
ALL THEIR INESTIMABLE GIFTS

PREFACE

This document has been prepared in the format of the manuscript plan in accordance to section 11-3 of the Graduate Manual at the University of Rhode Island. This dissertation has been divided into three sections.

Section I contains the statement of the problem and a brief introduction to the objectives of this research. Section II forms the central part of this dissertation and is composed of eight manuscripts written in the format prescribed by the scientific journal to which they have been or will be submitted for publication. Section III contains appendices that include the list of publications, methodological details and supplementary material useful for clearer understanding of the results described in the preceding manuscripts. One of the appendices presents a brief chronological list of some key milestones in the history of food and drug regulation in the United States to assist the reader in developing a historical perspective. An overall summary of conclusions and bibliography for the entire dissertation follows this section.

TABLE OF CONTENTS

ABSTRACT	
ACKNOWLEDGEMENTS	iv
PREFACE	vii
LIST OF TABLES	x
LIST OF FIGURES	xii
SECTION I	1
Introduction	2
Objectives	6
SECTION II	8
MANUSCRIPT I: Examination of regulatory aspects of nonprescription medicines in the United States	9
MANUSCRIPT II: Examination of global regulatory aspects of nonprescription medicines	39
MANUSCRIPT III: OTC switch case history evaluation: Nicorette®	85
MANUSCRIPT IV: OTC switch case history evaluation: Metaproterenol	107
MANUSCRIPT V: Evaluation of proposed OTC switch for Lovastatin	118
MANUSCRIPT VI: Examination of proposed OTC status for nonsedating antihistamines	150
MANUSCRIPT VII: Attitudes and opinions towards regulatory aspects of nonprescription medicines: Part 1	169
MANUSCRIPT VIII: Attitudes and opinions towards regulatory aspects of nonprescription medicines: Part 2	200

TABLE OF CONTENTS

SECTION III	223
APPENDIX A: List of publications	224
APPENDIX B: Supporting information and methodological details related to the dissertation in electronic format provided on an attached compact disk	225
APPENDIX C: A brief chronological list of some key milestones in the history of food and drug regulation in the United States relevant to this dissertation	226
SUMMARY OF CONCLUSIONS	237
BIBLIOGRAPHY	245

LIST OF TABLES

Description	Page
-------------	------

MANUSCRIPT I

Table 1: Trends in alternative medicine use in the United States, 1990-1997 (data summarized from reference 7)	34
Table 2: Description of scientific evidence necessary for justifying reclassification of an approved prescription drug product to the OTC status in the United States	35
Table 3: Specific issues upon which FDA intends to solicit comments through the over-the-counter drug products public hearing	37

MANUSCRIPT II

Table 1: Summary of the schedules relevant to substances for human use as per the Australian classification system	75
Table 2: Summary of the assessment factors used in scheduling nonprescription medicines for human use as per the Australian classification system	76
Table 3: Summary of the factors used for listing drugs for human use in Schedule F (subject to prescription control) as per the Canadian classification system	77
Table 4: Description of factors that serve as the foundational basis for scheduling drugs in Canada	78
Table 5: Summary of suitable evidence required for justification of a rescheduling application submitted to NDPSC review in Australia	79
Table 6: Steps in the regulatory amendment process to de-schedule drugs to nonprescription status at the federal level in Canada	80
Table 7: Summary of data requirements for a reclassification application in The European Union	81
Table 8: Classification of proprietary drugs (nonprescription medicines) in Japan	82
Table 9: Data required for approval of nonprescription drugs in Japan	83
Table 10: Description of clinical trial requirements for nonprescription medicines in Japan	84

MANUSCRIPT III

Table 1: Description of proposed OTC Nicorette [®] product	104
Table 2: Summary of types of studies and information presented by the sponsor	105
Table 3: List of questions presented to the Advisory Committees for voting by the FDA in relation to the proposed Nicorette OTC switch	106

LIST OF TABLES

MANUSCRIPT IV

Table 1: List of questions posed by FDA to its Advisory Committees on the proposed OTC status for lovastatin 10 mg	149
--	-----

MANUSCRIPT VII

Table 1: Distribution of survey respondents classified by profession, country and knowledge of nonprescription regulations	195
--	-----

Tables 2A to 2D: Summary of responses to survey statements and descriptive statistics along with description of legends	196
---	-----

MANUSCRIPT VIII

Table 1: Description of participants interviewed for this study	220
---	-----

Table 2: Description of participants whose written statements were used for this study	222
--	-----

LIST OF FIGURES

Description

Page

MANUSCRIPT I

Figure 1: Summary of regulatory mechanisms through which an approved prescription drug product may be reclassified as an OTC drug product. As all prescription drugs are considered to be new drugs, box 2 does not contain any products	36
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SECTION I

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INTRODUCTION

In recent years, self-medication products have undergone a dramatic change due to the advent of herbal medicines, dietary supplements, nutraceuticals and health foods in addition to traditional nonprescription medicines and the increasing societal preferences towards greater individual control over the use of medicines (1,2). Conventional regulations seem inadequate to address the complex challenges and regulatory needs of today's self-medication arena leading to a regulatory vacuum. Some important discrepancies associated with the regulation of nonprescription medicines are:

(1) Globally, there exists no uniformity in the classification of nonprescription medicines. For example, over-the-counter (OTC), pharmacy medicine (P) and quasi-drugs (QD) are variations of nonprescription drug products available within the developed world.

(2) Scientific methodologies to assess the risks and benefit to individuals/general public health associated with use of OTC drug products (in terms of pharmacological profile of active moieties, their dosage or disease conditions) are unclear. There exist inadequacies to facilitate an efficient Rx-to-OTC switch driven by science-based, data-driven decision making processes.

(3) The role of the US Food and Drug Administration (FDA) in the Rx-to-OTC switch process in the absence of support from a sponsor is unclear.

Globally, the role and importance of nonprescription medicines in healthcare delivery is rapidly increasing due to the shift in societal attitudes towards self-medication and the associated cost-savings (3). In 1999, global sales of nonprescription medicines grew by 4.7% to US \$49.2 billion following the trend in recent years (4). The

growing global interest in self-medication and related economic benefits emphasize the importance of and necessity for a regulatory framework developed on the basis of sound scientific principles. Hence, this area is beginning to receive much attention from regulatory authorities, academia and professional/industry/trade organizations.

Also, the US FDA recently initiated a comprehensive review of the Agency's approach to regulating over-the-counter (OTC) drug products, that is ongoing and conducted a public hearing on this subject in June, 2000 (5). The purpose of the hearing was to solicit information from interested persons including scientists, professional groups and consumers. FDA's intention is to elicit comments on general issues regarding the status of OTC drug products, including the criteria the Agency should consider in rendering decisions on OTC availability of drugs, the classes of products, if any, that are not currently available OTC that should or should not be available OTC, how FDA can be assured that consumers understand the issues relating to OTC availability of drug products, how rational treatment decisions are affected by coexisting prescription and OTC therapies for a given disease, whether the current structure for marketing OTC products in the United States is adequate, and FDA's role in switching products from prescription to OTC status.

As per the Food and Drug Administration Modernization Act of 1997 (FDAMA), the US FDA held a series of public meetings in the summer of 1999 to obtain stakeholder views on how FDA can best meet its statutory obligations (6). In response, the Consumer Healthcare Products Association (CHPA) representing producers of nonprescription medicines and dietary supplements provided comments emphasizing the need for science-based regulatory framework for OTC medicines and

especially for the OTC switch process (7). These recent developments clearly justify the need for a detailed investigation of the regulatory aspects of OTC medicines with an emphasis on the Rx-to-OTC switch process.

This investigation addresses issues central to the regulatory aspects of OTC products. Considering the rapidly increasing global interest in responsible self-medication and the recent call for proposals from all interested parties by the US FDA on this topic, the timing of this study is very appropriate.

This investigation was conducted in three phases. Phase-1 involved the completion of: (a) a critical review of existing literature related to this investigation, and (b) information retrieval. During information retrieval, data describing the regulatory aspects of nonprescription medicines from various sources (including governmental regulatory authorities, trade/industry organizations, pharmaceutical companies and academia) were collected. Special emphasis was placed on collecting data related to the regulatory environments in United States, Canada, United Kingdom, The European Union, Japan and Australia. The completion of a critical, comparative evaluation of the regulatory frameworks across these countries marked the culmination of Phase-1. During Phase-2, case history analyses of drugs to represent a broad variety of Rx-to-OTC switches of contemporary interest within the US FDA context were examined. A secondary goal was to use these switch case studies to illustrate and analyze the application of Rx-to-OTC switch regulatory policy by the US FDA in the recent past. An appropriate number of drugs that were selected and studied are: (a) successful Rx-to-OTC switch (nicotine) (b) unsuccessful Rx-to-OTC switch (lovastatin) (c) initially approved Rx-to-OTC switch that was later reverted to Rx status (metaproterenol), and

(d) switch proposal initiated by a party other than the sponsor (non-sedating antihistamines). In Phase-3, the attitudes/opinions of the academic/professional community with expertise in nonprescription medicines across the US, Canada, UK and Australia on important questions posed by the US FDA were measured using an internet-based electronic survey questionnaire instrument. The responses of the survey participants were analyzed using appropriate statistical techniques. Also, the opinions of a small group of key opinion leaders across the previously mentioned four countries selected to represent the diverse viewpoints of stakeholders in this area were studied using telephone interviews. Overall, conclusions and inferences based on the comparative literature review, investigation of OTC switch case histories, analysis of survey questionnaire and telephone interview responses have been summarized to provide data-based, rational answers to questions posed by the US FDA.

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OBJECTIVES

The salient objectives of this study are listed below:

1. Perform an examination of the current global regulatory environment of nonprescription medicines. To conduct a detailed review and comparative evaluation of the US OTC regulations with those in other comparable developed nations (Australia, United Kingdom, European Union, Canada and Japan) by focusing on: (a) classification of medicines (for human use) and the underlying scientific rationale, and (b) regulatory policies affecting prescription to nonprescription reclassification (Rx-to-OTC switch) of medicines.
2. To study the application of US FDA OTC switch regulatory policy in the recent past to obtain learning and make inferences that may be applied to answer questions of current interest, using the following case history evaluations as illustrative examples:
 - a. Nicotine: a habit-forming drug that was successfully switched to OTC status.
 - b. Metaproterenol: a bronchodilator that was switched to OTC status by the FDA upon its own initiative and was later reverted back to prescription status.
 - c. Lovastatin: a cholesterol-lowering drug for which OTC status was requested and was not granted by the US FDA.
 - d. Second generation nonsedating antihistamines: loratadine, fexofenidine and cetirizine, three nonsedating antihistamines for which OTC status was requested by an independent party over the objections of the

manufacturers that are currently being considered for OTC status by the US FDA.

3. To measure the attitudes and opinions of experts in the area of nonprescription medicines in the US, UK, Canada and Australia on regulatory aspects of OTC medicines on which the US FDA has requested information through the administration of an internet based electronic survey questionnaire instrument and telephone interviews.
4. To use the observations, learning and results of the above examinations in the development of rational, data-based recommendations related to important regulatory questions on OTC medicines in the US FDA context.

SECTION II

2344

MANUSCRIPT I

EXAMINATION OF REGULATORY ASPECTS OF NONPRESCRIPTION MEDICINES IN THE UNITED STATES

Abstract

Growing patient involvement in diagnosis and treatment coupled with easy information access has increased interest in self-care and use of nonprescription medicines globally. The mounting interest in self-medication and potential economic benefits highlight the importance of and necessity for a regulatory framework developed on sound scientific principles. Hence, this area is receiving attention from regulatory authorities, academia and industry. The US Food and Drug Administration (FDA) recently announced a public hearing to evaluate its approach to regulating over-the-counter (OTC) drug products. The main objectives of this study are to review and compare: (a) classification of medicines, and (b) regulatory policies affecting prescription to nonprescription reclassification (Rx-to-OTC switch) of medicines, among major developed nations along with the World Health Organization (WHO) perspective. This paper presents an analysis of the regulatory environment in the United States.

Introduction

Growing patient involvement in the diagnosis and treatment of common ailments coupled with easy access to reliable information is leading to increasing interest in self-care and the use of nonprescription medicines worldwide. Nonprescription medicines now account for about 60% of all medications used in the United States and may be used to treat or cure about 400 ailments (1). In 1999, global sales of nonprescription medicines grew by 4.7% to US \$49.2 billion in line with the trend in recent years (2). The role and importance of nonprescription medicines in healthcare delivery all over the world is rapidly increasing due to the shift in attitude towards self-medication and the potential cost-savings (3). In recent years, the landscape of self-medication products has undergone a dramatic change due to the rapid advent of herbal medicines, dietary supplements, nutraceuticals and health foods in addition to traditional "pharmaceutical" nonprescription medicines (4). Conventional regulations were not designed to address the complex challenges and regulatory requirements of today's self-medication arena precipitating the need for concomitant evolution in regulatory policies.

The growing global interest in self-medication and related economic benefits accentuate the importance of and necessity for a regulatory framework developed on the basis of sound scientific principles. Hence, this area is beginning to receive much attention from global regulatory authorities, academia and related industry/professional organizations. The US Food and Drug Administration (FDA) recently announced a public hearing to evaluate the Agency's approach to regulating over-the-counter (OTC)

drug products (5). The purpose of the hearing is to solicit information from interested persons including scientists, professional groups and consumers.

Consequently, an examination of the current global regulatory environment of nonprescription medicines has been undertaken to review and compare the US OTC regulations with those in other comparable developed nations. The central focus of this exegesis is on: (a) classification of medicines (for human use) and the underlying scientific rationale, and (b) regulatory policies affecting prescription to nonprescription reclassification (Rx-to-OTC switch) of medicines, in the United States.

State of nonprescription medicines

The usual perception of nonprescription medicines as pharmaceutical medicines available without a prescription has undergone a dramatic change due to the rapid advent of complementary and alternative medicines (CAM). This shift in societal preferences has increased the scope of nonprescription medicines to include dietary supplements, herbal medicines, folk remedies and other traditional ethnic medicines (6). Eisenberg et.al. studied the trends in CAM use in the US between 1990 and 1997 (7). Their results show that CAM use and expenditures substantially increased between 1990 and 1997 attributable primarily to an increase in the proportion of population seeking alternative therapies and the pertinent data is summarized in table 1.

The significance of nonprescription medicines in public health care is also reaching unprecedented levels. In the US, approximately 60% of all medicine dosage units consumed are nonprescription medicines. Of approximately 3.5 billion health problems treated annually in the US, some 2 billion (57%) are treated with a nonprescription medicine. About a third (33%) of all nonprescription medicines are

consumed by the rapidly growing demographic group of older Americans. The benefit-cost ratio of responsibly used nonprescription medicines is very favorable. Nonprescription medicines account for less than three cents of every dollar spent on healthcare in the US, yet the benefit derived is vast (8). These observations are in agreement with global trends in support of self-medication. In the United Kingdom, evidence indicates that growing numbers of general practitioners and consumers are in favor of increased responsible self-medication. Positive support by physicians for self-medication is growing and research shows that more than half the general practitioners expect to increase their recommendations of nonprescription medicines in the next year (9). It is reasonable to conclude that due to the onset of the information age, change in consumer preferences and the availability of new nonprescription medicines that were previously unavailable, the significance of nonprescription medicines in overall health care is bound to increase in the future.

Regulation of nonprescription medicines in the US

In the United States, the original Food and Drugs Act was passed in 1906 prohibiting interstate commerce in misbranded and adulterated foods, drinks and drugs (10,11). This law only ensured purity and did not address the important issue of truthfulness of health claims among other inadequacies. Following the Sulfanilamide tragedy, The Federal Food, Drug and Cosmetic Act (FD&C Act) was passed in 1938 as the foundation of present day drug laws (12). This law contained many new provisions such as, requiring new drugs to be shown safe before marketing (starting a new system of drug regulation), eliminating the earlier requirement to prove intent to defraud in

drug misbranding cases, requiring human drugs to bear label warnings against habit formation and requiring FDA to enforce the law.

Arguably, the most important amendment to the FD&C Act in this context is the Durham-Humphrey Amendment of 1951. This amendment clarified the dispensing obligations of the pharmacist by defining the kinds of drugs that cannot be safely used without medical supervision and restricting their sale to prescription by a licensed practitioner (13). This amendment also serves as the foundational basis for the current classification system of drug products in the United States into, prescription medicine and nonprescription medicine (or OTC). Section 503(b)(1) of FD&C Act states:

"A drug intended for use by man which -

(A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

(B) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug; shall be dispensed only

- (i) upon a written prescription of a practitioner licensed by law to administer such drug, or*
- (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or*
- (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist.*

The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale."

Hence, the need for medical supervision and prescription requirement for a drug product may arise due to: (a) the drug characteristics or the method of use necessary for its safe use, or, (b) the new drug application (Section 505 of FD&C Act) under which it received approval. An implication of section 503(b)(1) that needs emphasis is that, only

drugs meeting above stated conditions require the additional control of medical supervision and prescription requirement, otherwise they may be sold without a prescription. Alternately stated, drug products are inherently presumed to be nonprescription unless otherwise required, as per FD&C Act. This assertion may be tersely stated as, "*if it can be OTC, it must be OTC*" to illustrate the inherent bias for "nonprescriptionness" arising from the law and is critical in the comprehension of this classification system (4).

Another important legislative development in this context is the Kefauver-Harris Drug Amendments of 1962, enacted as a result of the Thalidomide disaster (14). As per these amendments, manufacturers were required to prove the safety and efficacy of any new drug before its marketing, and FDA approval of the new drug application (NDA) became a necessary prerequisite to marketing. These amendments required an unprecedented program of accountability from the manufacturers. To fulfill its obligations under these amendments, the FDA contracted with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4000 drugs approved only on the basis of safety between 1938 and 1962, under the so called Drug Efficacy Study Implementation or DESI Review in 1966 (11).

Further the FDA in 1972, initiated rulemaking procedures to determine which nonprescription medicines (The OTC Drug Review) can be generally recognized among qualified experts as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use (5). Through the OTC Drug review process, FDA established monographs for classes of nonprescription medicines (such as antacids etc.) that were generally recognized as safe and effective and not misbranded

when the products contained the ingredients and are labeled as per the monograph. OTC drug monographs describe the active ingredients, amount of drug, formulation, labeling and other general requirements for drugs to be lawfully sold OTC. In all 722 active ingredients for different uses were reviewed by 17 expert advisory panels through the public review and comment process of OTC Review. About a third of all the drugs reviewed were found to be generally recognized as safe and effective for OTC use (15).

The OTC Drug Review marked the onset of the era of rational regulation of nonprescription medicines on the basis of sound scientific evidence. It is generally agreed that the OTC Review created: (a) a claims structure based on scientific evidence and rational regulatory policy (b) a safety standard that is equal to or higher than that for prescription medicines (c) an increase in consumer confidence by ensuring nonprescription medicines deliver the benefits advertised, and (d) an emphasis on comprehensive labeling, with clearly defined policies for OTC warnings (4).

Considering the rapidly growing segment of the nonprescription medicine market that is comprised of CAM, it is important to also discuss the state of their regulation in the US. Kottke has recently published an elaborate review of the scientific basis and the regulatory state of nutraceutical products. It is suggested that readers peruse that report and other references for a comprehensive study of this subject (16,17,18,19). FDA's concern to regulate vitamins and dietary products in a manner similar to drug regulation has been ongoing for many years. But, unfortunately such attempts have only been unsuccessful, for instance, FDA withdrew proposed regulation requiring minimum and maximum levels of dietary supplements in the face of severe consumer protest in 1962 and federal courts disallowed FDA from regulating high

dosage vitamins as drugs based on the toxic impacts of such products in late 1970s. An immensely counteracting force restraining FDA's attempts from regulating dietary supplements and vitamins based on scientific evidence has been the lack of Congressional support due to intense advocacy by the dietary supplement industry. Such lobbying and effective grass roots level campaigning led to the enactment of the Dietary Supplement Health and Education Act (DSHEA) of 1994 causing dramatic changes in the regulatory framework. Most importantly, DSHEA resulted in: (a) a clear, but very broad, definition for a "dietary supplement" (b) changing the rules surrounding the labeling of dietary supplements, and (c) shifting the burden of proof of product safety from the manufacturer to the FDA.

As per DSHEA, a dietary supplement is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients. Further, the term is defined to include products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license. This very broad definition has had the unintended consequence of including even prescription medicines under the term "dietary supplements" raising public health concerns (17,18). Cholestin[®] is a red yeast rice product marketed as a dietary supplement, and is a natural source of lovastatin which is the active drug in the prescription medicine Mevacor[®] used for lowering cholesterol levels. Before DSHEA, FDA contended that "labeling" of dietary

supplements included not only the actual product label, but also any other written, printed or graphic matter accompanying the product. DSHEA explicitly exempted from "labeling", any such accompanying written matter provided that such written matter is truthful and not misleading, effectively preventing the FDA from regulating supplements as drugs based on the claims made in accompanying material about cure, mitigation, treatment or prevention of any disease. As a result of such promotional literature being permissible, studies have found that significant proportions of public believe, quite often wrongfully, the ability of supplements in being helpful with illnesses (20).

The shifting of burden of proof of product safety from the manufacturer to the FDA is in stark contrast to the conventional regulatory philosophy of FDA with drugs (wherein a manufacturer has to demonstrate product safety and efficacy in a premarket review) and has left FDA with the authority only for postmarket surveillance. This observation is particularly important as per recent evidence showing an increasing number of adverse event reports associated with the use of supplements (21). Further, studies also show that frequently public fails to inform their physicians of the use of supplements, leading to an increase in potential for adverse events (7,21). The issue of claims for dietary supplements remains to be an extremely contentious one (22).

Clearly, the rigorousness of regulatory evaluation of alternative medicines and supplements does not match the same for traditional prescription and nonprescription medicines that are preapproved on the basis of elaborate scientific data and evidence to prove product safety and efficacy. Further, the level of scientific advancement amongst traditional pharmaceutical nonprescription medicines is much greater than that of

supplements and alternative medicines. To strengthen the scientific foundation of alternative medicines, DSHEA has mandated the creation of an office within the National Institutes of Health (NIH) to explore the potential role of supplements to improve health care in the U.S. The office will also need to: (a) promote scientific study of supplements and their value in preventing chronic diseases (b) collect and compile scientific research, including data from foreign sources and the NIH-Office of Alternative Medicine (c) serve as a scientific adviser to Secretary of Health and Human Services and FDA, and (d) compile a database of scientific research on supplements and individual nutrients. These initiatives will, hopefully, help strengthen the scientific foundation driving regulatory policy concerning nontraditional nonprescription medicines. It is also hoped that as traditional pharmaceutical companies enter the arena of developing supplement products for economic benefits, they will extend their science-based and data driven product development philosophy to the supplements industry.

Reclassification of medicinal products in the US

Reclassification is the process of removing the prescription requirement and need for medical supervision for a marketed drug product (for human use) that was previously available only through a legitimate prescription and making it available over-the-counter. It is commonly referred to as "Rx-to-OTC switch" or simply "the switch". One major factor responsible for the rapid growth of responsible self-medication via use of nonprescription medicines is the recent reclassification of previously prescription medicines to OTC status that have been very successful, both medically and commercially. It may be helpful to divide this subject into, (a) regulatory

mechanisms through which a marketed prescription drug product may be reclassified as an OTC product, and (b) scientific evidence or data required in support of the petition requesting such a reclassification.

An excellent review of the Rx-to-OTC switch process, related procedures and the underlying statutory scheme has been presented by Wion (23). There are essentially four regulatory mechanisms through which reclassification may be achieved. They are:

- filing of an NDA (NDA approach)
- filing of a supplement to an approved NDA (sNDA approach)
- as per section 503(b)(3) of FD&C Act (switch regulation approach), and
- the OTC Drug Review (monograph approach).

In the NDA approach, either a traditional NDA (per section 505(b)(1) of FD&C Act) or a "paper" NDA (per section 505(b)(2) of FD&C Act) may be filed. The NDA route is suitable in the event where the proposed OTC product is of a lesser strength or for a different indication than its prescription counterpart, in which event efficacy and safety need to be established. The switch of Ibuprofen at the 200 mg dose to OTC status utilized the NDA approach for reclassification. Under the sNDA approach, a supplement to the original NDA under which the drug product was approved may be filed demonstrating the suitability of the product for OTC use to request reclassification. Benylin[®] cough syrup containing diphenhydramine hydrochloride was switched to OTC status using the sNDA approach. It must be noted that upon successful reclassification

via the NDA approach or sNDA approach, the drug product in the OTC status is considered to be a new drug.

The Durham-Humphrey amendments to the FD&C Act were enacted to state clearly the criteria useful in limiting drug products to sale by prescription only. These amendments eliminated the confusion prevalent before their enactment and are contained in section 503 of FD&C Act. Section 503(b)(3) of FD&C Act states:

"The Secretary may by regulation remove drugs subject to sections 502(d) and 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health."

This statement authorizes the Secretary of Department of Health and Human Services to remove the prescription requirement and need for medical supervision arising from NDA approval for prescription use (section 505) or for habit-forming drugs (section 502(d)) or the drug characteristics or method of its use necessary for its safe use (section 503(b)(1)) when the determination is made that such requirements are not needed to protect public health. Using this authority, FDA in 1956 issued the so-called "switch regulation" that is now codified in 21 CFR 310.200. Subsection (b) of 21 CFR 310.200 states:

"Prescription-exemption procedure.

(b) Prescription-exemption procedure for drugs limited by a new drug application. Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling. A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(C) of the act may be initiated by the Commissioner or by any interested person. Any interested person may file a petition seeking such exemption, which petition may be pursuant to part 10 of this chapter, or in the form of a supplement to an approved new drug application."

Hence, using the switch regulation the FDA or any interested person may initiate the reclassification process and drugs so switched to OTC status also are considered to be new drugs (see 21 CFR 310.200(c)). Prior to 1971, the FDA switched 25 ingredients to OTC status using the switch regulation (listed in 21 CFR 310.201). The NDA or sNDA approaches to reclassification are useful if there exist only a few manufacturers of the drug product whereas broad rulemaking and promulgating a switch regulation is preferred if the product has a large number of manufacturers. Subsection (e) of 21 CFR 310.200 states:

"Prescription-exemption procedure.

(e) Prescription-exemption procedure of OTC drug review. A drug limited to prescription use under section 503(b)(1)(C) of the act may also be exempted from prescription-dispensing requirements by the procedure set forth in Sec. 330.13 of this chapter."

21 CFR 330.13 describes the conditions for marketing ingredients recommended for over-the-counter (OTC) use under the OTC Drug Review (monograph approach). As discussed earlier, this is the mechanism that FDA used in 1972 to initiate the OTC Drug review through the use of Expert Advisory Panels for the establishment of OTC monographs for classes of drugs (such as antacids). Concurrent to the OTC review, the FDA also invited views from interested persons on prescription drugs that may be suitable for OTC use, initiating the deliberation process for potential switches. The administrative procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs are described in 21 CFR 330.10. The monograph rulemaking process was essentially a three-step process, where: (a) FDA Commissioner appointed advisory review panels for each designated area of OTC drugs and all areas of OTC drugs were considered. Also,

requests for data and views on OTC drugs were made. (b) The review panels upon completion of their evaluation submitted to the FDA Commissioner their report of recommendations covering all areas of OTC drugs reviewed. They classified all the reviewed OTC drugs into the following three categories, (i) Category I, where category of drugs were found to be suitable for OTC use and a recommended monograph was established (ii) Category II, a statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding, and (iii) Category III, a statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition and for which further testing is therefore required. (c) The FDA then used the panel's recommendations to publish initially, tentative final monographs for public evaluation that were later published as final monographs upon consideration of public views.

The drugs switched to OTC status via the monograph approach, in contrast to the other approaches, are not considered as new drugs. A summary of the regulatory mechanisms that may be employed to facilitate reclassification of an approved prescription human drug to OTC status in the US has been presented in figure 1. In recent times, the NDA approach has been the most frequently used mechanism for obtaining approval for an Rx-to-OTC switch. MAPP 6020.5 in the Manual of Policies and Procedures of Center for Drug Evaluation and Research establishes the Office of Review Management (ORM) procedures for assessing investigational new drugs (IND)

and marketing applications for OTC drugs to be marketed under the authority of an approved NDA, either initially or as Rx-to-OTC switch (24). These procedures describe how the ORM interacts with the sponsors who intend to market OTC drug products (initially or as a switch) during the IND/NDA review, and the relevant post approval oversight necessary.

The FDA has not published any formal guidance describing the data requirements (scientific evidence) it deems as necessary for a switch petition to receive approval. The FDA has, instead, taken the position that switch petitions will be reviewed on a case-by-case basis, based on the weight of scientific evidence presented to demonstrate general suitability for OTC use. Hence, there does not exist any universally applicable guidance useful in the preparation of a switch petition. However, helpful insights into the general requirements and standards for safety, effectiveness and labeling in the OTC context may be gained by studying the procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs described in 21 CFR 330.10. These procedures were codified in 21 CFR 330.10(a)(4) as instructions to the advisory review panels as:

"(4) Standards for safety, effectiveness, and labeling. The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and the final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in Sec. 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs."

Further, elaboration of specific criteria used by the FDA to determine the adequacy of scientific evidence (with regards to safety, effectiveness and labeling) required for reclassification may be found in the presentation of the Director of Office of Drug Standards at the US FDA, who elucidated the above statements as per his comprehension during a workshop on reclassification (25). Also, the Senior Vice President of Consumer Health Products Association (CHPA, the trade association representing the manufacturers and distributors of nonprescription medicines and dietary

supplements with members representing over 90 percent of retail sales in the US OTC marketplace) recently authored an excellent article describing, as per his view, the specific scientific data requirements applicable in the determination of "OTCness" of a drug being considered for reclassification (26). The scientific evidence deemed necessary for successful reclassification as per these two articles have been summarized in table 2.

Contemporary topics of interest and importance

In describing the scope of the public hearing earlier this year, FDA solicited comments on general issues regarding OTC drug products such as: (a) criteria used to decide on the availability of OTC drug products (b) classes of products that should or should not be available OTC (c) consumer understanding of OTC issues (d) selection of treatment (e) current US OTC marketing system, and (f) FDA's role in switching products from prescription to OTC status. The specific issues under each of these general categories upon which the FDA requested views have been listed in table 3. The list of issues presented by the FDA is not complete and other important topics also need to be addressed.

The scope of this public hearing as published by the FDA focuses on regulation of OTC drug products treating pharmaceutical nonprescription medicines in an isolated manner. As stated, the notion of OTC drug products being construed only as traditional pharmaceutical medicines is changing fast. It is perhaps beneficial to review and examine the regulatory aspects of OTC drug products considering them as a portion of the present day self-medication armamentarium that includes dietary supplements and other traditional medicines. In this regard, initiatives to market at least some of the

nontraditional medicines as regular OTC drug products by subjecting them to the same rigorous scientific evaluation and review criteria should be promoted upon careful consideration. Otherwise, FDA's general product approval philosophy based only on sound scientific evidence will continue to be compromised.

Another important factor, the influence of which upon availability of new OTC drug products and reclassification needs to be clarified, is the direct-to-consumer marketing of prescription drug products. Some questions that need to be addressed are: Are any of such drug products suitable candidates for reclassification?; If, only a physician may write a prescription upon diagnosis, why are such promotional activities aimed at consumers creating a "quasi self-medication" possibility?; In the process of a consumer initiated enquiry resulting in a responsible medication choice upon consultation with a physician, can the physician be replaced by the pharmacist, at least in some cases? The lack of dedicated initiatives aiming at global harmonization of reclassification policy is a cause for concern as globalization is a rising trend among the industry. Subsequently, some key issues that need to be addressed are: Why is there variation in the dosage strength of certain medicines approved for OTC use between nations? Why are certain medicines OTC in some nations, whereas they are prescription only in others? Is it possible to develop and establish globally acceptable monographs for OTC drug products, at least within the developed world? Lastly, the application of information technology to promote and achieve responsible self-medication through enhanced and effective consumer education needs to be explored. The authors intend to address some of the above issues in this, and subsequent articles.

One noteworthy issue concerns the clarity of FDA's role in the reclassification process. In particular, FDA asks: *Under what circumstances should FDA actively propose OTC marketing for a drug in the absence of support from a sponsor?, and, Should FDA be more active initiating switches of prescription products for OTC use?* Before addressing these questions, FDA's legal authority to initiate a switch proposal under the current framework needs to be examined. Of the four regulatory mechanisms discussed through which reclassification may be achieved, FDA has unambiguous authority to initiate a switch proposal via the switch regulation as per 21 CFR 310.200 (b) and section 503(b)(3) of FD&C Act. As for the NDA or sNDA approaches, section 505 of FD&C Act describes the details of the new drug application and related processes. More specifically, subsection 505(b)(1) while explaining the details of the NDA filing process states:

"(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;"

It is important to focus on the term "person" to understand who qualifies for filing an NDA. Subsection 201(b)(e) of the FD&C Act in defining this term states:

"The term "person" includes individual, partnership, corporation, and association".

It does not appear that FDA fits into the definition of "person" as per FD&C Act, as FDA is not an individual, partnership, corporation or an association. Under this premise, it seems reasonable to conclude that the Act did not envision FDA itself filing an NDA, hence disallowing FDA to do so. Consequently, FDA does not qualify to file an NDA

or an sNDA seeking reclassification. Finally, under the OTC Drug Review procedures stated in 21 CFR 330.10 there do not exist any statements suggesting unambiguously the authority of FDA to initiate a switch process. 21 CFR 330.10(a)(2) states:

"Request for data and views. The Commissioner will publish a notice in the Federal Register requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs....."

Again, use of the "interested persons" terminology perhaps disqualifies FDA from submitting switch proposals via the monograph system and delegates to FDA the role of a facilitator rather than a participant. From this discussion, it may be inferred that FDA has legal authority to promulgate regulation for reclassification to OTC status of prescription medicines only via the switch regulation mechanism under the current legislative framework. At this juncture, it is appropriate to consider the issue of whether FDA should exercise its authority to switch products only in collaboration with the sponsor. In the interest of public health and fairness to industry, the FDA should undertake any initiatives to switch products only in collaboration with the sponsor based on their active support. This approach is most desirable and offers the benefit of FDA being able to utilize the sponsor's vast knowledge database related to the development and marketing of the product.

The undesirable action of FDA switching a product despite the sponsor's objection to do so should be carried out only under very limited and unusual circumstances. Such a situation may be enormous and overwhelming public support for OTC availability of a certain product, assuming it meets all the safety, effectiveness and labeling standards required of OTC products. The inherent difficulty in such an

approach would be that the burden of proving suitability for OTC use would lie on FDA and such a task may be formidable in the absence of support from the sponsor. Further, it is very difficult to envision FDA being able to prove suitability for OTC use without access to data from the original NDA (which is the sponsor's intellectual property). Further, FDA should also present a cogent argument demonstrating the need for such radical regulatory action and subsequent benefit to overall public health. This should be done in an open and transparent process that includes all interested persons prior to such a decision taking effect.

Conclusion

The role and significance of nonprescription medicines in overall health care delivery worldwide is mounting rapidly due to changing social preferences and associated economic benefits. The US FDA has initiated the desirable program of announcing a public hearing to evaluate its approach to regulating OTC products. In this regard, the authors have undertaken a comparative evaluation of regulatory aspects of nonprescription medicines within major developed nations. An examination of the regulatory environment of nonprescription medicines in the United States shows that there exists a wide gap in the scientific basis supporting the regulatory principles for traditional pharmaceutical nonprescription medicines and alternative medicines or herbal remedies. There exist many challenging issues related to the reclassification of products to OTC status in the United States. The authors believe that FDA should invoke its authority to switch products to OTC status in collaboration with the sponsor using their support and expertise.

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Table 1: Trends in Alternative Medicine Use in the United States, 1990-1997 (data summarized from reference 7)

<i>Measured Outcome</i>	<i>1990</i>	<i>1997</i>
Use of at least one form of alternative therapy in the previous year	33.8% of population surveyed	42.1% of population surveyed
Probability of users visiting an alternative medicine practitioner	36.3%	46.3%
Total visits to an alternative medicine practitioner (extrapolated to US population)	427 million	629 million *
Concurrent use of prescription medications with herbal remedies and/or high dose vitamins	Not available	15 million adults (18.4% of all prescription users)
Estimated expenditures for alternative medicine professional services	Not available	US \$ 21.2 billion

* This estimate exceeds the total visits to all the US primary care physicians

Table 2: Description of scientific evidence necessary for justifying reclassification of an approved prescription drug product to the OTC status in the United States

<i>Safety</i>	<i>Effectiveness</i>	<i>Labeling</i>
<ol style="list-style-type: none"> 1. Toxicity and potential for harmful effect <ul style="list-style-type: none"> • Clinical pharmacology data (LD50, subacute and chronic toxicity) • Pharmacokinetics (absorption, excretion, accumulation, metabolism, protein binding) • Potential drug interactions • Carcinogenicity/teratogenicity/mutagenicity(especially in chronic use situations) • Complete analysis of adverse event data from postmarketing experience, controlled clinical trials, voluntary reports during marketing and experience with overdoses not only in the United States but also from foreign sources such as Medicines Control Agency of U.K. • Assessment of safety in special populations such as pediatrics, geriatrics and pregnant women 2. Overall benefit/risk assessment <ul style="list-style-type: none"> • Low incidence of overall adverse events or substantial side effects under use with adequate directions • Possible reduced dosage (with demonstrated effectiveness) • Low potential for harm from abuse upon widespread availability 3. Abuse/misuse potential <ul style="list-style-type: none"> • Can the conditions be self-treated without prior diagnosis by a physician? (or) • Can the conditions be self-treated after diagnosis by a physician? 4. Are routine medical examination or laboratory work needed for continued safe use of the drug? <ul style="list-style-type: none"> • Do these factors alone preclude the drug from OTC availability? 5. Method of use and collateral measures necessary to use <ul style="list-style-type: none"> • Can the condition being treated be self-diagnosed? if not, • Are the symptoms to be treated self-recognizable? • Can the condition be self-treated? 	<ol style="list-style-type: none"> 1. The proposed OTC use should be substantially similar to the approved prescription use. 2. Controlled Clinical investigations in the target populations proving clinically significant relief of the type claimed in labeling. 3. If OTC use is at a lower dosage than approved for prescription, then efficacy needs to be demonstrated at the new dosage. 4. How broad of a patient population was included in the prescription clinical trial? 5. Corroboration of effectiveness under partially controlled or uncontrolled studies by qualified experts and reports of significant human experience during marketing (so called "actual use study" setting). 	<ol style="list-style-type: none"> 1. Intended uses and results of the product and ability to control that labeling. 2. Adequate directions for proper use. 3. Adequate warning against use in those pathological conditions, or by children, or against unsafe dosage or methods or duration of administration or application. 4. Warnings against unsafe use, side effects, and adverse reactions should be stated to facilitate accurate communication to individuals of low comprehension under conditions of customary purchase and use. These warnings must be scientifically documented, clinically significant and important to the safe and effective use of the product by the consumer. 5. Include general OTC pregnancy/nursing warnings unless drug is exempt and limitations on how long the OTC drug product should be used before seeking medical attention.

Figure 1: Summary of regulatory mechanisms through which an approved prescription drug product may be reclassified as an OTC drug product. As all prescription drugs are considered to be new drugs, box 2 does not contain any products

	<i>Rx (prescription)</i>	<i>OTC (nonprescription)</i>
<i>New drug</i>	<i>Box 1</i>	<i>Box 3</i> <i>Box 1 to Box 3</i> (through NDA, sNDA or the switch regulation approaches)
<i>Not a new drug</i>	<i>Box 2</i> (Empty)	<i>Box 4</i> <i>Box 1 to Box 4</i> (through the OTC Drug Review Process)

Table 3: Specific issues upon which FDA intends to solicit comments through the Over-the-counter Drug Products Public Hearing

<i>Criteria</i>	<i>Classes of Products</i>	<i>Consumer Understanding</i>	<i>Selection of Treatment</i>	<i>OTC Marketing system and FDA's role in switching</i>
<ul style="list-style-type: none"> • What criteria should FDA consider in rendering decisions on OTC availability of drug products? • What types of drugs are or are not appropriate for OTC distribution? • What types of diseases are or are not suitable for treatment with products marketed OTC (e.g., chronic illnesses; diseases that require initial diagnosis by a physician; diseases that if left untreated, or are inadequately treated, can lead to serious morbidity or mortality)? • How should the risks and benefits to 	<ul style="list-style-type: none"> • Are there specific classes of products that are not currently marketed OTC that should be available OTC? • Are there specific classes of products that should not be available OTC? What specific concerns do these classes raise? (Examples of specific classes that might be discussed in brief include: Diuretics, antihypertensive agents, cholesterol-lowering drugs, oral antidiabetic agents, treatments for osteoporosis (including its prevention), antimicrobials, and oral contraceptives. 	<ul style="list-style-type: none"> • How can FDA be assured of consumer understanding of the benefits and risks of specific drug products and the ability of consumers to use products safely and effectively were the drug products to be marketed OTC? • What methodologies can be employed to demonstrate consumer understanding? • How can information on efficacy be adequately conveyed to consumers through labeling? • Can prevention claims encourage ill-advised behavior, and if so, how could this potential be minimized? 	<ul style="list-style-type: none"> • How can rational selection be ensured when there are coexisting prescription and OTC therapies for a given disease? • In an environment with coexisting products, what are the most effective means to ensure that patients know the best ways to treat their illnesses? • How should the availability of OTC options and prescription options for the same indication be reconciled? • How should the availability of a "better" OTC product, in terms of efficacy or safety, affect the status of products 	<ul style="list-style-type: none"> • Is the current structure for marketing OTC products in the United States adequate? • What lessons can we learn from different OTC marketing systems? • What can be learned from the countries and those U.S. states where some nonprescription drug products are sold OTC and others are sold "behind the counter"? • Under what circumstances should FDA actively propose OTC marketing for a drug in the absence of support from the

Table 3: Specific issues upon which FDA intends to solicit comments through the Over-the-counter Drug Products Public Hearing

<i>Criteria</i>	<i>Classes of Products</i>	<i>Consumer Understanding</i>	<i>Selection of Treatment</i>	<i>OTC Marketing system and FDA's role in switching</i>
<p>individuals and risks and benefits to the public health be assessed and weighed in any decision on OTC marketing? For example, how should the Agency balance the potential benefits of OTC antimicrobial agents with the potential risks to society at large of the development of resistant organisms associated with increased, and potentially improper, use?</p>			<p>already on the OTC market for treatment of the same condition?</p> <ul style="list-style-type: none"> Should older therapies that may provide less benefit or more risk be removed from the OTC market, or should the labeling be revised? Suppose the more effective drug is more difficult to use and must remain prescription -might that encourage use of the less satisfactory drug? 	<p>drug sponsor?</p> <ul style="list-style-type: none"> Should FDA be more active in initiating switches of prescription products to OTC use?

MANUSCRIPT II

EXAMINATION OF GLOBAL REGULATORY ASPECTS OF NONPRESCRIPTION MEDICINES

Abstract

Globally, rising interest in self-medication and related economic benefits highlight the importance of and necessity for a regulatory framework developed on sound scientific principles for nonprescription medicines. This area is receiving attention from regulatory authorities, academia and industry. The US Food and Drug Administration (FDA) recently announced a public hearing to evaluate its approach to regulating over-the-counter (OTC) drug products. This study aims to review and compare: (a) classification of medicines, and (b) regulatory policies affecting prescription to nonprescription reclassification (Rx-to-OTC switch) of medicines, among major developed nations along with the World Health Organization (WHO) perspective. This paper presents an analysis of the contemporary regulatory environment in Australia, Canada, European Union, United Kingdom and Japan with the WHO position. The regulatory model in the United States has been evaluated with that in comparable developed nations to draw pertinent inferences.

Introduction

Growing global interest in self-medication and potential economic benefits draw attention to the necessity for a regulatory framework developed on the basis of sound scientific principles. Hence, this area is beginning to receive much attention from global regulatory authorities, academia, industry and other stakeholders. The US Food and Drug Administration (FDA) recently announced a public hearing to evaluate the Agency's approach to regulating over-the-counter (OTC) drug products and solicit information from interested persons including scientists professional groups, and consumers (1). Specifically, two important questions that FDA asks are: *(a) Is the current structure for marketing OTC products in the United States adequate? (b) What lessons can we learn from different OTC marketing systems?*

Consequently, an examination of the current global regulatory environment of nonprescription medicines has been undertaken to review and compare the US OTC regulations with those in other comparable developed nations. The central focus of this exegesis is on: (a) classification of medicines (for human use) and the underlying scientific rationale, and (b) regulatory policies affecting prescription to nonprescription reclassification (Rx-to-OTC switch) of medicines. An earlier article examined the regulatory environment in the United States and this article presents the same in Australia, Canada, European Union, United Kingdom and Japan along with the World Health Organization (WHO) perspective (2). The overall object is to learn from various global regulatory models and draw inferences that may be beneficial when applied in the United States context.

Classification of medicines

Australia

In Australia, the Therapeutic Goods Act of 1989 (TG Act) aims at providing a national framework for the regulation of therapeutic goods to ensure their quality, safety, efficacy and timely availability. The Therapeutic Goods Administration (TGA) as part of the Commonwealth Department of Health and Aged Care has the responsibility for administering the Act and ensuring that the necessary evaluation and assessment procedures are conducted to enable access to the latest treatments available that are safe, effective and of good quality. A general introduction to the regulatory process for all medicines in Australia and other pertinent matters including the role of TGA is presented in one of TGA publications (3).

The TGA uses a *risk-management approach* to regulating medicines that forms the basis of the Australian classification system. Accordingly, *risk* is determined by a number of factors such as: (a) the medicine containing a scheduled substance (discussed later) (b) medicine's use can result in significant side-effects (c) the medicine is used to treat life-threatening or very serious illnesses, and (d) there may be any adverse effects from chronic use or inappropriate self-medication. Essentially, any product for which therapeutic claims may be made must be either *listed* or *registered* in the Australian Register of Therapeutic Goods (ARTG) before being marketed in Australia. ARTG was established under Part 3 of the Therapeutic Goods Act to include a computer database of information about therapeutic goods for human use that are approved for supply in, or export from Australia (4).

Listed medicines are considered to be of lower risk than registered medicines, so the regulations allow for sponsors to self-evaluate (in terms of efficacy) their products in some situations and majority of listed medicines are used for self-medication without a prescription being required. Listed medicines only contain well known established ingredients with long history of use, most complementary medicines (such as herbal, vitamin and mineral products), medicines that are intended only for export and if they do not contain any scheduled substances. The TGA assesses listed medicines only for quality, safety and not efficacy, but sponsors are legally mandated to hold information to substantiate their product's claims. *Registered medicines* are assessed as having a higher level of risk. The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors being required to provide comprehensive safety, quality and efficacy data prior to receiving marketing approval. Registered medicines include both prescription and nonprescription medicines (to include both traditional pharmaceutical OTC products and complementary or alternative medicines). In rare instances, some products may qualify for exemption from being listed or registered in the ARTG.

The registration process for entry into ARTG is determined in part by the poisons classification system of the National Drugs and Poisons Schedule Committee (NDPSC) for inclusion in the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) based on their toxicity, purpose of use, potential for abuse, safety in use and need for the substance. The National Drugs and Poisons Schedule Committee (NDPSC) is a standing committee of the Australian Health Minister's Advisory Council (AHMAC) and determines the classification and thus, the appropriate *schedule*, of a substance (NDPSC also determines classification of veterinary drugs, agricultural and

household chemicals in addition to human drugs). The SUSDP includes a number of provisions (such as labeling, packaging and advertising) that relate to the level of control intended to apply to the scheduled substances (3,5). NDPSC decisions have no effect and do not attract controls until they are included in state and territory legislation. While generally, NDPSC decisions are automatically adopted by reference in most jurisdictions (unless action is specifically taken not to accept a specific scheduling decision), others require publication in the Australian Gazette before scheduling decisions come into force.

The NDPSC has published guidelines for classification of drugs and poisons that it follows in rendering decisions related to the scheduling of substances (6). As per this guidance, scheduling applications are reviewed by considering all relevant information like: (a) need for access to a substance in context of its toxicity relative to substances available for a similar purpose (b) purpose of use (c) method of use (d) dosage form or formulation type (e) extent, pattern of use and proposed use in the community (f) misuse (g) drug interactions and adverse events (h) package type and size to prevent childhood poisoning, and (i) bioaccumulation. Based on this scientific rationale, a total of nine schedules have been developed by the NDPSC. Of these nine schedules, schedules 2,3,4 and 8 (S2, S3, S4 and S8) describe medicines for human use, S1 is not presently under use and S9 covers prohibited substances (S5, S6 and S7 describe poisons for agricultural, veterinary and domestic use). Among human drugs, substances classified under S2 and S3 do not require a prescription whereas availability of S4 and S8 substances is through prescription only. Further, NDPSC describes for each schedule, the general description, purpose, assessment factors (drug's characteristics,

indications for use), public health consideration and marketing experience. A summary of the schedules relevant to substances for human use is presented in table 1 and the assessment factors used in the scheduling of human medicines are tabulated in table 2.

Canada

The Health Protection Branch (HPB) of Health Canada is responsible for drug quality, safety and efficacy. It regulates drugs imported into and manufactured for sale in Canada, and drug distribution including conditions of sale. At the federal level, drug products are classified into prescription and nonprescription products (7). Schedule F to the *Food and Drug Regulations* is a listing of chemical entities or classes of drugs that, with exceptions, are required by regulation to be sold under prescription (8). The factors that are used by HPB to restrict drugs to Schedule F are presented in table 3.

Additionally, Provincial Pharmacy Acts, enforced by provincial pharmacy regulatory authorities (PRAs), regulate the profession and the practice of pharmacy and may further specify conditions of sale. Within these acts, drugs are classified into categories (called *drug schedules*) with conditions imposed on their sale (9). Prior to 1995, five provinces had provisions in their Pharmacy Acts controlling the distribution of drugs that provided additional levels of control to those already contained in the federal legislation and they did not regulate additional location of sale. This situation led to disharmony in how drugs were scheduled and controlled across Canada.

The necessity for drug schedule harmonization in Canada was addressed and the Canadian Pharmaceutical Association (CPhA) proposed a mechanism be established to assess the existing scheduling system and consider the benefits derived from greater consistency in drug scheduling. This proposal also recommended the assessment of the

legislation, procedures and criteria generating these schedules. Subsequently, as a result of the collaborative efforts between HPB, PRAs, CPhA and other interested parties the final report "*Harmonized Drug Schedules in Canada*" was released and subsequently endorsed by the National Association of Pharmacy Regulatory Authorities (NAPRA). This proposal called for a national drug-scheduling model, to align the provincial drug schedules so that the conditions for the sale of drugs would be consistent across Canada. This harmonized national model consists of three schedules or four categories of drugs, consistent inclusion factors for each schedule, a standard process for scheduling, and a national advisory committee (National Drug Scheduling Advisory Committee, NDSAC) to make scheduling placement recommendations to the provincial regulatory authorities (7,10).

- *Schedule I drugs require a prescription for sale and are provided to the public by the pharmacist following the diagnosis and professional intervention of a practitioner. The sale is controlled in a regulated environment as defined by provincial pharmacy legislation.*
- *Schedule II drugs, while less strictly regulated, do require professional intervention from the pharmacist at the point of sale and possibly referral to a practitioner. While a prescription is not required, the drugs are available only from the pharmacist and must be retained within an area of the pharmacy where there is no public access and no opportunity for patient self-selection.*
- *Schedule III drugs may present risks to certain populations in self-selection. Although available without a prescription, these drugs are to be sold from the self-*

selection area of the pharmacy that is operated under the direct supervision of the pharmacist, subject to any local professional discretionary requirements which may increase the degree of control. Such an environment is accessible to the patient and clearly identified as the "professional services area" of the pharmacy. The pharmacist is available, accessible and approachable to assist the patient in making an appropriate self-medication selection.

- *Unscheduled drugs can be sold without professional supervision. Adequate information is available for the patient to make a safe and effective choice and labeling is deemed sufficient to ensure the appropriate use of the drug. These drugs are not included in Schedules I, II or III and may be sold from any retail outlet.*

NAPRA has developed and published national standards of practice for pharmacists, corresponding to the level of professional intervention and advice necessary for the safe and effective use of drugs by the Canadian consumer. The National Drug Scheduling Advisory Committee (NDSAC) functions to make drug scheduling recommendations to NAPRA and its member provincial pharmacy regulatory authorities. The model for making drug scheduling recommendations embodies a "cascading principle" in which a drug is first assessed using the factors for Schedule I. Should sufficient factors pertain, the drug remains in this schedule. If not, the drug is compared to the factors for Schedule II and if appropriate, subsequently assessed against the factors for Schedule III. Should the drug not meet the factors for any schedule, it becomes unscheduled. The *factors* that serve as the foundational basis for scheduling decisions by the NDSAC have been summarized in table 4.

The European Union

In 1995, a new European System for the authorization of medicinal products came into operation. After several years of cooperation between national regulatory authorities at European Union (EU) level, the EU Council adopted three directives and a regulation in June-1993 when combined form the legal basis of the system. The European Agency for the Evaluation of Medicinal Products (EMEA) was established by the Council Regulation (EEC) 2309/93. The European system offers, a centralized procedure (covering all member nations) and a decentralized procedure (covering a specific member nation that may then be extended to other member nations via mutual recognition) for authorization of medicinal products.

In the European Union, Council Directive 92/26/EEC of 31 March-1992 describes in detail the classification system for supply of medicinal products for human use (11,12). Article 1(1) of this Directive classifies medicinal products into, medicinal products subject to medical prescription and medicinal products not subject to medical prescription. Further, Article 3(1) of this Directive provides the criteria under which medicinal products are subject to medical prescription and states:

Medicinal products shall be subject to medical prescription where they:

- *are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or*
- *are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or*
- *contain substances or preparations thereof of the activity and/or side effects of which require further investigation, or*

- *are normally prescribed by a doctor to be administered parenterally*

Also, Article 3(2) and Article 3(3) of this Directive state the necessary criteria for the sub-category of medicinal products that should be subject to *special medical prescription* or *restricted medical prescription* as may be required in certain member States. Article 4 of this Directive states:

Medicinal products not subject to prescription shall be those which do not meet the criteria listed in Article 3.

Thus, the Directive implicitly states that medicinal products should be subject to a prescription only when they meet the specifically defined criteria. Hence, the European Union classifies medicinal products into two categories, prescription medicines and nonprescription medicines, with the prescription requirement being applicable only when medicines meet certain defined criteria.

The United Kingdom

In the United Kingdom, Medicines Control Agency (MCA) is an Executive Agency of the Department of Health responsible to promote and safeguard public health through ensuring appropriate standards of safety, quality and efficacy for all medicines on the UK market. Additionally, the Agency is required to advise Ministers on policy relating to pharmaceuticals and regulatory systems and assist Ministers in achieving their high level objectives on health. The EU Directive on classification of medicines has been implemented in the United Kingdom. Medicinal products are classified into three different categories (13,14):

1. *Prescription-only Medicines (POM under section 59 of the Medicines Act, 1968): Ingredients limited to prescription supply are listed in The Prescription*

Only Medicines (Human Use) Order, 1997. This order specifies three categories of POM: parenteral products, controlled drugs and radioactive medicinal products. There are two other ways in which substances or products may be made POM. These are either by listing the substance in Schedule 1 of the POM Order or temporarily through the first Marketing Authorization (MA) for a new product.

- 2. General Sale List Medicines (GSL under section 51 of the Medicines Act, 1968): Medicines that contain ingredients on the General Sale List (The Medicines (Products other than Veterinary Drugs) General Sales List Order, 1984) are nonprescription medicines that may be sold from any lockable shop. GSL may be appropriate for medicines "which can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist" and "where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sales would be a convenience for the purchaser".*
- 3. Pharmacy Medicines (P): Any medicine that is not a POM or a GSL medicine is classified as pharmacy medicine. These medicines can be sold only from pharmacies under the supervision of a pharmacist. There is no list of these medicines in UK legislation.*

Japan

Drugs are classified into prescription drugs, non-prescription drugs (or proprietary drugs) and quasi-drugs (15). Nonprescription drugs are defined as those, which have a mild action and a high degree of safety if used correctly within a fixed

range of directions and dosage. They can be purchased directly from a pharmacy or a drugstore and used freely in self-medication by the consumers.

The examination for approval of proprietary drugs is based on the following principles (16):

- *The ingredients and quantities of proprietary drugs should be within a scope that assures the safety and efficacy of the products. Their action should be mild, products having a strong action or causing habituation or dependence should not be included.*
- *Their indications should be within the scope of preventing or treating minor diseases or maintenance and improvement of health. Diseases deemed to be treated by physicians should not be recognized as indications of proprietary drugs. Their indications should be mainly described by the symptoms that are easily understandable to the general public.*
- *Directions for administration, dosage and dosage forms shall be described in such a manner as to be easily understood by the general public on their own judgment. Products that may cause misuse or abuse, and those in such dosage forms (such as injections) as not used safely and effectively without the direction of physicians or other specialists are not recommended as proprietary drugs.*

Proprietary drugs are divided into six classes according to conditions in the approval application (such as ingredients, quantity, indications) and have been summarized in table 8 (16,17). Also, the data requirements and clinical trial data necessary for the registration for each class of proprietary drugs have been presented in

tables 9 and 10 respectively. Quasi-drugs as stipulated by the law are: (a) products having fixed purposes of use (b) products having a mild action on the human body, and (c) products other than instruments and apparatus. For a product to be designated as a quasi-drug all three conditions must be satisfied (18). Quasi-drugs have been specified for:

- Prevention of nausea and other indispositions, foul breath or body odor
- Prevention of prickly heat, sore and the like
- Prevention of loss of hair, promotion of hair growth or removal of hair
- Eradication or repellence of rats, flies, mosquitoes, fleas etc. for the health of man or other animals
- Other articles designated by the Minister of Health and Welfare (MHW) as similar to the items specified above

To facilitate rapid examination of proprietary drug approval applications, the MHW at the national level has been transferring the authority to prefectural governors, provided they adhere to uniform examinations as per established standards. Only the MHW may approve prescription medicines and quasi-drugs whereas nonprescription medicines may be approved either by the MHW or by the prefectural governments (15). Recently, the MHW approved fifteen categories of medicines under the quasi-drug status. These products are for minor ailments (sore throat, stomach discomfort), vitamins/minerals and for external use (topical ointments) in general. The distribution system in Japan is rather unique as about 66% of all prescription medicines are both

written and dispensed by physicians or dentists and only 1 in 3 prescription medicines is dispensed by pharmacists. Quasi-drugs may be sold at any retail outlet. Nonprescription medicines are sold through a variety of outlets such as a pharmacy, drugstore with a pharmacist and drugstore without a pharmacist. Additionally, outlets with special limited license and for household distribution also exist but are relatively uncommon.

Reclassification of medicines

Australia

Reclassification (or *rescheduling*) of medicines in Australia is also governed by NDPSC guidelines for classification of medicines and poisons (6). The process of rescheduling may be initiated by the evaluating Agency (TGA), product sponsor, state and territory authorities and occasionally by NDPSC itself. If an applicant believes that they can justify an alternative schedule entry for any medicine, an application may be submitted for review to the NDPSC with suitable evidence. For rescheduling of a drug substance from prescription only (S4) to a lower nonprescription (S2 or S3) or exempt from scheduling, NDPSC usually requires at least two years of local clinical use or local post-marketing surveillance of the drug substance before the proposal is considered. Suitable evidence for rescheduling could include: (a) evidence from comparable nations where the drug substance is available without a prescription (b) relevant public exposure information in other nations with a population base greater than Australia (c) any available information from post-marketing surveillance (local and overseas) (d) any relevant previous Australian consideration of scheduling of the drug substance, (e) any relevant Australian experience with the drug including a different route of administration. If the rescheduling application is for a new indication, then applications

need to be submitted to obtain approvals from the TGA and NDPSC. A detailed tabulation of suitable evidence justifying a rescheduling application is presented in table 5.

Canada

Reclassification (or *de-scheduling*) to nonprescription status in Canada has been addressed by the HPB in an information letter issued in June-1990 (19). The purpose of this information letter was to inform interested parties of the data requirements for applications to remove drugs for human use from Schedule F to the Food and Drug Regulations and outline the internal mechanism for handling such applications. Applications must demonstrate that a favorable ratio exists between the benefit to patients that will occur versus the risk to their health that may be inherent in permitting the nonprescription sale of the drug product. HPB requests the following information for assessment of the reclassification applications:

- *Efficacy data for new indications and safety data*

Efficacy data will be required if the indications of use or dosage differ from those approved for prescription use. A summary of all animal and human clinical safety data, including data that may have been part of an original submission and the data accumulated after the product's introduction.

- *Drug adverse reaction data*

A summary of all known domestic and foreign adverse drug reaction reports since the introduction of the medicinal ingredient, adverse effects with their frequency and the dose at which they occurred. Any adverse effects that could require patient

monitoring by a physician should be clearly described. Any potential for misuse or abuse and actual occurrences should also be discussed.

- *Labeling*

All proposed nonprescription labeling and promotional material demonstrating that the safe and effective use of the product can be assured by nonprescription labeling rather than depending upon the professional judgment of a physician. Appropriate cautions and contraindications must be addressed in lay terms.

- *Chemistry and manufacturing data*

Differences from the original submission and supplements must be identified. Chemistry and manufacturing data will be required where they differ from the prescription drug.

- *Market data*

Date of introduction of the prescription drug in the Canadian market and a summary of sales data must be included. If the product in consideration was not the first product introduced as a prescription drug, then date of introduction of the first product also must be provided. A summary of international market status (countries where requests for prescription or nonprescription status have been made, approved, rejected or are pending) is required. If a request has been refused, the reason for refusal is required. If the request was approved, the date of introduction in that market and confirmation that the product is currently marketed is required.

Additionally, the Drug Evaluation Unit of the HPB also published an information pamphlet on the subject of prescription to nonprescription switches in April-1999 (20). In this publication, HPB took the position that the switch process be

initiated by the manufacturer only, through the filing a supplemental new drug submission (SNDS) with HPB performing the assessment of the evidence provided to determine the suitability of the product and its indication for OTC use. The factors to be considered while evaluating the suitability for a switch and the data requirements for switch SNDS have also been briefly listed in this pamphlet. Also, HPB recently finalized revised guidelines for preparing submissions seeking to change the status of a drug from prescription to nonprescription. These guidelines for a switch divide switches into two types, Type I and Type II, based on the nature of the switch and complexity of the review.

Type I switch is for drugs which have same strength, dose, dosage form, indication and route of administration as the prescription product. Type I switches usually do not require the submission of new clinical trials or chemistry and manufacturing data. The review is mainly of the safety profile and whether self-medication is effective. Type II switch is for drugs which have a change in, the indication, dosage form, strength or dose, route of administration, relative to the prescription product. Hence, a type II switch request requires data from clinical trials to support the new strength or dosage formulation as a nonprescription product.

Removal of drugs from Schedule F, or addition of a qualifier to Schedule F (for dual status products) requires the promulgation of a regulatory amendment which is subject to federal regulatory process and involves several stages and levels of approvals, that include the Minister and the Governor-in-Council who are advised by the Special Committee of Council (SCC). The steps involved in the regulatory amendment process are outlined in table 6. A switch becomes law at the federal level once registered at the

SCC. After the drug is reclassified at the federal level, each province must then determine how the product will be sold and this determination is made by the National Drug Scheduling Advisory Committee (NDSAC) at the provincial level as discussed earlier.

The European Union

Reclassification within the EU has been addressed by the issuance of a guideline on changing the classification for the supply of a medicinal product for human use in September-1998 (21). This guideline is divided into two parts. Part one concerns the criteria for classifying a medicinal product as subject to medical prescription or not. Part two describes the data requirements for an application requesting reclassification of a prescription product to nonprescription status. As per this guideline, suitability of a medicinal product for nonprescription status is elaborated by examining the converse of each criterion (discussed earlier) that justifies the prescription requirement. A medicinal product not subject to a prescription should have the following characteristics under each specified attribute:

Direct danger/safety profile

- Low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties
- Low risk of serious type A adverse reactions (those that result from exaggeration of a drug's expected pharmacological actions when given in the usual therapeutic dose; normally dose-dependent) in the general population
- Very low risk of serious type B reactions (those that represent a novel response not expected from known pharmacological action)

- No interactions with commonly used medicines which can produce serious adverse reactions

Indirect danger/safety profile

- No indirect danger such as hiding/masking an underlying condition requiring medical attention and supervision even when the product is used as directed. Nonprescription medicines should be approved primarily for short-term treatment when the possibility of "masking" could occur.
- No increased risk of resistance to product with a wider use of a product within the general population to such an extent that the usefulness of any medicinal product is likely to be compromised.

Self-assessment

- Conditions or symptoms should be such that can be correctly assessed by the patient and the product can be used without medical supervision. Consumer communication may be facilitated by the use of written information, advice of pharmacist and other appropriate sources.
- The natural course of the disease, the condition, the duration of symptoms and their reoccurrence and consequences should be correctly self-assessable.
- Contraindications, interactions, warnings and precautions should be those that can be understood by the consumer.

Risk and consequences of incorrect use

- Absence of a high incidence of conditions listed as contraindications, precautions or warnings or a high rate of usage of interacting drugs in the population in case of

patients likely to use the medicine that may increase the incidence and risk of misuse.

- Low danger to health if the patient uses the product where it is not indicated or uses it for a longer period than recommended or exceeds the recommended dose or fails to heed warnings or contraindications.

Patient information

- Leaflet and label must contribute effectively to safe and effective use of medicine and should be sufficient so that it substitutes for absence of medical supervision. All information should be provided in layman's terms and prominently presented in the leaflet. Leaflet and label should describe in equal prominence when and when not the product should be used.

Known incorrect use

- If known incorrect uses exist, then such a product may not be considered for nonprescription medicine status. Similarly, products with low experience, where marketing authorization was only recently granted or when further investigation is required should also be not considered for nonprescription medicine status. Further, post-marketing information in an uncontrolled environment should be examined while reclassification.

Recent authorization/limited experience

- For reclassification at a new dose, in a new strength or using a new route of administration further investigation is necessary. At a lower strength, efficacy should be demonstrated. A re-evaluation of the risk to benefit ratio is necessary

under the proposed conditions of nonprescription status. The same is true when a combination of two or more active ingredients is considered.

Other considerations

- No parenteral products or products classified as special or restricted prescription products under Council Directive 92/26/EEC.
- Pack size should be decided in relation to the intended length of the treatment. Packages should be child resistant in nature and generally in restricted sizes as a possible safeguard against misuse.

Part two of the EU guideline describes the data requirements and documentation concerning safety and efficacy in support of an application for reclassification. This is usually dependent on the nature of the active substance and the extent of changes to the existing marketing authorization. In all cases, an expert report should be provided taking a clear position and defending the proposal with scientific knowledge and demonstrate why none of the criteria that lead to the prescription requirement should be applicable. In addition to scientific data addressing all points related to determining the suitability of the product for nonprescription status, other requirements summarized in table 7 should also be included in the expert report.

The United Kingdom

In the United Kingdom, two types of reclassification are possible. The first type of reclassification is from prescription only medicine to pharmacy medicine status (POM to P) and the second type is from pharmacy medicine to general sales list (P to GSL). The UK Medicines Control Agency (MCA) has specified a set of guidelines related to each type of reclassification. The POM to P reclassification has been

explained in Medicines Act Leaflet 77 (MAL 77) (13) and the P to GSL reclassification is discussed in Medicines Act Leaflet 82 (MAL 82) (22).

For POM to P reclassification, MAL 77 describes the procedure for amendment of the POM Order applying to products that are prescription medicines because they contain one or more substances listed in Schedule 1 to the POM Order. Applications under this procedure may be submitted as a variation or a new abridged application. The variation route is appropriate if the marketing authorization (MA) holder has a product suitable for reclassification, the proposal to amend the POM Order should be accompanied by an application to vary the legal status of the product. Other product particulars may also need to be varied in order for a product to be suitable for reclassification. If reclassification is agreed, amendment to the POM Order will proceed and the MA will be appropriately varied to take effect when the POM Order comes into force. If an MA holder wishes to make a change, for example to introduce a new strength, which requires a new application, a new abridged application should be made. A new abridged application should also be made if the MA holder wishes to hold a separate MA for the P product. Also, any interested party such as a professional body that does not itself hold an MA may request the reclassification of a substance. The content of the applications should be similar to that of applications from MA holders. Since, Schedule 1 to the POM Order is substance based, amendment will usually affect the legal classification of products containing that substance. If the MA is in line with the amendment to the POM Order, the product becomes classified as pharmacy medicine. However, MA holders should apply to vary their MAs in accordance with the

amendment to the POM Order, and provide appropriately amended labeling and patient information leaflets for approval.

Following assessment of the application, advice from the Committee on Safety of Medicines (CSM) will usually be sought on the proposed reclassification. If the reclassification proposal is supported, wider interests are then consulted. Responses to the consultation are examined by the MCA whose advice is passed to Ministers. It is for the Ministers to determine, in the light of the advice received, whether the POM Order should be amended. If the CSM recommends that a request for reclassification be refused, the originator of the proposal will be notified as to which POM criteria have been considered to apply and the reasons for advising against the change, and will receive a copy of the assessment report.

As stated earlier, the EC Directive on the classification of medicines (92/26/EEC) has been implemented in the United Kingdom and incorporated into section 58A of the Medicines Act, 1968. Although the prescription criteria of Council Directive 92/26/EEC apply to all EC member states, the procedure for assigning prescription classification remains the responsibility of each individual member state. In the United Kingdom, the required documentation in support of a POM to P reclassification request is substantially similar to that described in the EU guidance on the same subject. Applications should contain the following key information that has been discussed in detail in the earlier section in the European Union context. The key elements to be addressed in the expert report must include:

- Consideration of reclassification proposal in relation to the four criteria for prescription control (reference to Article 3(1) of Council Directive 92/26/EEC)

- Summary of data relating to safety and where appropriate efficacy
- Proposed patient information (labeling and patient information leaflet)
- Clinical expert report.

MAL 82 provides guidance on pharmacy to general sale list (P to GSL) reclassification procedures and requirements. As discussed earlier, similar procedures, steps and possible routes as for POM to P reclassification also apply to P to GSL reclassification. But, substantial differences exist in the criteria applied to evaluate suitability for GSL and the contents of the supporting application. Criteria applied to evaluate suitability of human medicines for GSL has been defined earlier. The supporting application for a P to GSL reclassification must contain:

- *Expert report*
 - Clear demonstration in light of scientific knowledge why the GSL criteria must apply
 - Discussion of maximum dose, maximum daily dose and the indications suitable for use. Explanation of contra-indications, warnings, adverse reactions, interactions and problems of overdose and other misuse under GSL conditions.
 - Justification for the need for special handling precautions as being very small. Discussion of difficulties in the extrapolation of P to GSL use.
- *Data requirements*
 - Experience in exposure to substance should be considerable. GSL use suitable medicines should have been in P use for many years.

- Description of safety profile, to include, post-marketing surveillance/clinical studies, adverse drug reports under GSL conditions in UK and foreign nations. Comparison of safety with other approved GSL medicines for similar indications.
- New PK/PD or efficacy data are usually not required. Animal studies are also not required except under special circumstances.
- Complete analysis of any experience of therapeutic misuse or abuse that may be deliberate or accidental. Description of symptoms from overdose or misuse along with recommended treatments.
- Proposed patient information leaflets, labeling, pack size and any other changes in product presentation should be provided. Safety warnings such as limited duration treatment or the need to consult a doctor or pharmacist should be listed.

The guidance states that anthelmintics, parenteral products, drops/ointments for ophthalmic use, enemas, products for irrigation of wounds or of the bladder, vagina or rectum and products for administration to children that are preparations of aloxiprin or aspirin are not included in the GSL.

Japan

The procedures, application format and data requirements for registration and approval of nonprescription medicines, as discussed earlier, apply exactly and in same measure to reclassification application dossiers in Japan (18). The future course of MHW related to reclassification is presently under consideration and additional guidance (15) in the interim may be summarized as:

- The active ingredients proposed for switching application should have undergone complete re-examination or re-evaluation.
- Review of switch applications should be conducted upon serious consideration of the opinions of Central Pharmaceutical Affairs Council to determine whether the product is suitable for nonprescription medicines status. A rate of incidence of adverse medicine reactions, administration and dosage, actual examples of use of the medicine in foreign countries, results of either re-examination should be taken into consideration.
- To ensure appropriate use and safety of the medicine, conditions may be imposed at the time of approval such as to conduct post-marketing surveillance (PMS), directions on information provision and sales methods and advertising standards.
- Upon approval of the switch application, the product may be sold only in a pharmacy or a drugstore with a pharmacist.
- PMS of the prescription product and actual use trials (AUT) should be conducted to support switch applications. PMS should include two kinds of surveillance emphasize actual use/administration of proposed OTC drugs by subjects and adverse reactions documented after the product's launch.
- New clinical trials are required and should be carried out in at least five locations in Japan with not less than 150 cases even if the prescription product is considered for switching without any changes.

Health Organization perspective

The WHO finalized and published guidelines on the regulatory assessment of medicinal products for use in self-medication in March-2000 (23). This guidance states

that a medicinal product for self-medication should, at least, meet the following three criteria:

1. *Active ingredient: The active ingredient at the intended dose should have low inherent toxicity (no reproductive toxicity, genotoxic or carcinogenic properties relevant to human use, unless such hazard can be appropriately addressed by labeling).*
2. *Intended use: The intended use should be appropriate for self-medication. Use of the products should not unduly delay diagnosis and treatment of a condition requiring medical attention.*
3. *Product properties: The product should not have properties that make it undesirable. For example, it should not have an unfavorable adverse event profile, require a physician's supervision for monitoring during drug therapy, represent a significant risk of dependence or abuse or display other limiting characteristics such as interaction with commonly used medicines or foods that may result in serious adverse reactions.*

If the product meets these criteria, the following additional requirements may be applied:

- *The use of the product has been sufficiently extensive or in high enough volume.*
- *The product has been marketed on prescription for at least five years.*
- *Its adverse events give no cause for concern and their frequency has not increased unduly during the marketing period.*

A basic principle for the regulatory assessment, as per WHO guidance, is that the pharmacokinetics, pharmacodynamics, indications, safety, efficacy, toxic or

allergenic potential of a medicinal product should have been reasonably well established and documented in humans before its eligibility for use in self-medication can be evaluated. The general regulatory assessment approach should, in detailed terms, investigate the following five complementary aspects:

- Active substance and rationality of its indications
- Specific routes of administration, dosage forms and formulations
- Specific safeguards
- Suitability for self-medication status
- Labeling and package inserts and other information forming a basis for advertising and promotion

The guidance also provides details on the collection and regulatory assessment of evidence for medicinal products intended for nonprescription status hitherto available only on prescription. The objective of the regulatory assessment, while considering reclassification should be to form an opinion on the basis of evidence that will generally comprise:

- *The original regulatory data (chemistry, manufacturing, pharmaceutical, pharmacological, toxicological, clinical pharmacological, clinical trial, therapeutic efficacy and safety data)*

This is relevant only if the product is being considered for reclassification without any changes to the marketed prescription product. If the original animal investigations suggested severe risks (like carcinogenicity) the risks should be reassessed in light of subsequent experience in humans.

- *Clinical data obtained after the approval of the drug*

Trials performed according to current standards and relating closely to the proposed use in self-medication should be accorded the greatest weight.

- *Drug utilization and consumption data*

This is helpful in determining the way in which the product has hitherto been employed by physicians (volume of use, major indications in practice, precautions normally taken) and particularly in interpreting alleged risks.

- *Reported adverse events/reactions and interactions*

This should be examined with respect to their profile, frequency and severity. Sources in which the evidence is critically assessed (especially in well controlled clinical studies or epidemiological studies) are preferable to those in which unevaluated observations of possible adverse reactions are accumulated. Data from sources that have collected adverse reactions information from different countries for long periods of time may be useful, in particular, from WHO's International Drug Monitoring Programme.

- *Current scientific data*

The pharmaceutical form and packaging should be considered, any available clinical studies, field data and market-related studies on consumer use of the product for self-medication should be examined.

Comparative evaluation

An evaluation of the regulatory systems for nonprescription medicines in comparable developed nations demonstrates the unequivocal recognition of their vital role in public health care. The basic scientific rationale used to designate nonprescription status to medicines is very similar within the considered models. But,

there exists wide variation in the categories of nonprescription medicines available in these markets. Some classification models (Australia, Canada, United Kingdom and Japan) recognize an intermediate class of nonprescription medicines, controlled by the pharmacist, whereas other models (the US and EU) do not. The issue of an intermediate, pharmacist-controlled nonprescription category being included within the US regulatory model has been quite controversial. The major proponent of an intermediate class of medicines has been the American Pharmaceutical Association, whereas the Consumer Health Products Association (CHPA, the trade association representing the manufacturers and distributors of nonprescription medicines and dietary supplements in the US OTC marketplace) has strongly opposed such a new class of medicines (24,25,26). The US General Accounting Office (GAO) upon congressional request in 1995 issued a report titled *"Nonprescription Drugs: Usefulness of a Restricted Sale Class has Not Been Demonstrated"* (27). To date, this is the most comprehensive study conducted in the US on this subject and performed a detailed investigation of drug classification/distribution systems across ten countries. The US GAO reached the conclusion that *"reliable and valid studies that examine the effect of drug distribution systems on overall health and healthcare system costs do not exist"*. This GAO conclusion clearly demonstrates the need for reliable, objective and valid studies through which useful information may be elicited to reach a definitive conclusion on this matter.

Although, the appropriate scientific principles used to categorize nonprescription medicines are remarkably similar across various regulatory systems, the end results of each classification system are highly variable. There exist many examples of the same drug substance being subject to conflicting status across the considered

regulatory models. Also, there exists wide variation in classification of the same drug substance based on dosage level. In Canada, UK and Australia, substance based lists of drugs subject to prescription control are maintained whereas in the US, such is not the case. The US approach of classification based only on the approved submissions, without any substance based lists, offers greater clarity. The OTC monograph system in the US that resulted from the OTC Drug Review benefits the pharmaceutical industry by simplifying the approval process. A similar system as the OTC monographs, on a global basis would benefit other regulatory systems also.

The scientific principles and the supporting data requirements based on which reclassification applications are reviewed are also remarkably similar in the regulatory systems studied here. As is the case with classification of drug substances, although the process and principles used for evaluation of reclassification request are quite similar, they have produced varying results for the same substance in different nations. Regulatory bodies in the US, Australia, Japan have taken the position that they can, themselves, initiate reclassification requests, whereas in Canada and the United Kingdom such requests should be initiated only by the holders of marketing approval or other interested bodies. All the regulatory models (Australia, Canada, UK, EU, Japan and WHO guidance) elaborated here have well-defined and structured data requirements that need to be submitted in support of reclassification requests. Such is not the case with the US FDA. Although, 21 CFR 330.10 does provide general insights into the requirements and standards for safety, effectiveness and labeling in the OTC context, the US FDA has not issued any specific guidance on the details of structure/format of the justification and the types of data required to prove suitability for

nonprescription use. An important lesson that would be very useful in the US context is that US FDA should develop a guidance document for industry describing the nature of data required for justification of a reclassification petition. Another major contrast relates to the possibility of new chemical entities (NCE) being marketed as nonprescription medicines (i.e. direct-to-OTC) if they meet all the necessary requirements. There is no uniformity among the various regulatory models on the duration for which a drug substance must be marketed as a prescription medicine before it may be considered for reclassification to nonprescription status. That duration in, Australia is two years, Canada is three years Japan is six years, and WHO regulations require five years. The UK and EU regulations also state that any NCE must be marketed as a prescription medicine for a substantial duration before reclassification may be considered. The US position on this issue is unique as no such requirement is explicitly stated, leaving open the possibility of an NCE being marketed directly on OTC status. Reclassification requests in some markets (Australia, Canada and Japan) require approval from regulatory bodies at both federal and state level. In the US and UK such is not the case. Necessity to obtain approval from federal and state level agencies (especially in Canada) is burdensome for the industry. Under the US and UK models, approval is obtained primarily at the federal level which is efficient and desirable.

Conclusion

Nonprescription medicines in major developed nations have been recognized as crucial to efficient public health care. Accordingly, Australia, Canada, the United Kingdom, the European Union and Japan have all established regulatory frameworks

based on scientific principles for classifying drug substances under the nonprescription status and reclassifying prescription medicines as nonprescription medicines. However, there exists significant opportunity for improvement of current regulatory systems within these nations to enhance efficiency of regulatory review, convenience to drug manufacturers and consumer access to nonprescription medicines. In this regard, the US OTC regulatory system should seriously consider issuing guidance to industry on specific data requirements for reclassification petitions and investigating the merits of an intermediate pharmacy-class of nonprescription medicines.

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Table 1: Summary of the schedules relevant to substances for human use as per the Australian classification system

<i>Schedule</i>	<i>Description</i>	<i>Purpose</i>
Schedule Two (S2, nonprescription medicine)	<ul style="list-style-type: none"> • Substantially safe but counseling available if necessary • For minor ailments that can be easily recognized by the consumer and do not require medical diagnosis 	To allow effective drugs for which pharmacist advice on use may be required by the consumer to be available without a prescription.
Schedule Three (S3, nonprescription medicine)	<ul style="list-style-type: none"> • Substantially safe but require professional advice by a pharmacist • Use of which requires pharmacist advice, management or monitoring • For ailments or symptoms which can be identified by a consumer and verified by a pharmacist and do not require medical diagnosis or only require initial medical diagnosis without need for close medical management 	To allow effective drugs which require professional advice on use by the consumer to be available from the pharmacist without a prescription.
Schedule Four (S4, prescription medicine)	<ul style="list-style-type: none"> • Use of which requires professional medical, veterinary or dental management/monitoring • For ailments or symptoms that require professional medical, veterinary or dental diagnosis or management • The safety or efficacy of which may require further evaluation • Which are new therapeutic substances 	To make available drugs the use, supply and prescribing of which should be by registered medical, veterinary or dental practitioners and supply of which should be on prescription
Schedule Eight (S8, prescription medicine)	<ul style="list-style-type: none"> • Which are dependence producing • Which are likely to be abused or misused 	To allow potent drugs to be available for medicinal use with restrictions on manufacturing, trade, distribution, possession and use to prevent abuse, addiction and dependence

Table 2: Summary of the assessment factors used in scheduling nonprescription medicines for human use as per the Australian classification system

<i>Schedule</i>	<i>Assessment factors</i>
S2- Nonprescripti on medicine (regular OTC products)	<ul style="list-style-type: none"> • Suitability for self treatment of a minor ailment or symptom capable of being monitored by the consumer • Extremely low abuse potential, low potential for harm from inappropriate use • Low adverse effects and contra-indications for which counseling is available • Low interactions with commonly used substances or food for which counseling is available • A wide therapeutic index and low risk of masking a serious disease and compromising medical management of a disease • Not require ongoing or close medical diagnosis or management • Easy recognition of ailment by consumer • Amenable to short term treatment and monitoring and self-management by consumer with counseling
S3- Nonprescripti on medicine (Pharmacist only medicine or behind-the- counter products)	<ul style="list-style-type: none"> • Low abuse potential, harm from inappropriate use, incidence of side-effects or adverse events likely to require medical intervention • Only common drug/food interactions that may be managed by a pharmacist • Medium to wide therapeutic index • Risk of masking a serious disease or compromising medical management can be managed by a pharmacist • Not require close medical management or direct supervision by a doctor • Ailment easily recognized with assistance of a pharmacist • Amenable to short term treatment and monitoring and self-management by consumer with assistance of a pharmacist

Table 3: Summary of the factors used for listing drugs for human use in Schedule F (subject to prescription control) as per the Canadian classification system

Drugs will be listed in Schedule F if:

- individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring are required;
- there is a narrow margin of safety between the therapeutic and toxic doses, especially in populations such as geriatrics, children and pregnant or nursing mothers;
- there are potential or known undesirable or severe side effects at normal therapeutic dosage levels;
- they are known by experimental data to induce toxicity in animals but have not been in clinical use long enough to establish the pattern or frequency of long-term toxic effects in humans;
- they are used in treatment of a serious disease easily misdiagnosed by the public;
- their use may mask other ailments;
- they have contributed to, or are likely to contribute to, the development of resistant strains of micro-organisms in humans;
- they possess a dependence or abuse potential that is likely to lead to harmful non-medical use;
- they possess a high level of risk relative to expected benefits; or
- they have a therapeutic effect based on recently elucidated pharmacological concepts, the consequences of which have not been established.

Exceptions will be considered for drugs which:

- are required to be readily available under emergency circumstances where it is not practical to obtain a prescription (such as adrenalin in insect bite kits);
- are rarely used without a practitioner's supervision, and where the need for free availability outweighs the need for protection under Schedule F (such as insulin and nitroglycerin); or
- have potential to produce dangerous interactions with other drugs or food constituents but effective labeling can minimize the risk.

Table 4: Description of factors that serve as the foundational basis for scheduling drugs in Canada

<p>Schedule I</p> <ul style="list-style-type: none"> • Indications for use of the drug are identifiable only by the practitioner. • Use of the drug requires adjunctive therapy or evaluation. • Use of the drug may produce dependency. • Serious adverse reactions to the drug are known to occur or have a recognized potential to occur at normal therapeutic dosage levels. • There exists a narrow margin of safety between the therapeutic and toxic dosages of the drug, either in the general population, or in identified subpopulations, or in patients with multiple medical problems. • Serious interactions of the drug are known to occur. • Use of the drug has contributed to, or is likely to contribute to, the development of resistant strains of microorganisms. • The mechanism of action of the drug is known but the consequences of widespread use are not adequately established. • The therapeutic effects of a newly released drug are based on new or unknown mechanisms of action, but the consequences of widespread use are not adequately established.
<p>Schedule II</p> <ul style="list-style-type: none"> • The initial need for a drug is normally identified by the practitioner, in addition chronic, recurrent, or subsequent therapy <u>must</u> be monitored by the pharmacist. • The drug must be readily available under exceptional circumstances when a prescription is not practical. • The drug is intended for administration in a health care setting or under direction of a health care professional, or is in an injectable dosage form and is not otherwise included in Schedule I. • Evidence of abuse of the drug has been reported, due to its inherent pharmacological action that has the potential for abuse. • The selection of the drug requires intervention by the pharmacist to confirm that an appropriate self-assessment has been made by the patient. • Use of the drug may delay recognition or mask the symptoms of serious disease. • The drug may cause important adverse reactions, including allergies, or interacts with other drugs, foods, or disease states that cannot be adequately addressed through product labeling. • Use of the drug requires reinforcement or an expansion of the directions for use, through pharmacist - patient dialogue. • The drug is a new ingredient for self-medication and monitoring by the pharmacist is necessary to facilitate observation and reporting of any unexpected event. • The maximum labeled dosage directions exceed the generally accepted or usual limits for Schedule III status.
<p>Schedule III</p> <ul style="list-style-type: none"> • The initial need for a drug is normally identified by the patient, physician, or pharmacist, but chronic, recurrent, or subsequent therapy can be monitored by the pharmacist. • The maximum recommended duration of use of the drug is limited and specified on the product label. • The maximum recommended duration of use of the drug is not specified on the label, but continued use may delay recognition or mask the symptoms of serious disease. • The drug is used to treat a persistent, chronic or recurring condition and the availability of the pharmacist to provide advice can promote appropriate use. • The drug is used for self-treatment of self-limiting ailments; however, where product selection has been identified as likely to cause patient confusion and the availability of the pharmacist to provide advice can promote appropriate use. • The drug demonstrates adverse effects, including allergies, or interacts with other drugs, foods, or disease states that can be identified in product labeling, but appropriate product selection and explanation of risk may require the advice of the pharmacist. • The drug is a new ingredient for self-selected self-medication and the availability of the pharmacist to provide advice can promote appropriate use. • The drug has inherent pharmacologic action that has the potential for non-medical use that may result in adverse patient outcomes. • The maximum labeled dosage directions exceed the generally accepted or usual limits for unscheduled status.

Table 5: Summary of suitable evidence required for justification of a rescheduling application submitted to NDPSC review in Australia

<p>Name of chemical/active constituent</p> <ul style="list-style-type: none"> • Its approved name • IUPAC name • All proprietary, non-proprietary or other names and code numbers 	<p>Toxicological database</p> <ul style="list-style-type: none"> • Toxicokinetics • Acute studies <ul style="list-style-type: none"> ▪ Lethality or lower toxic dose ▪ Skin & eye irritancy ▪ Skin sensitization ▪ Corrosivity • Repeat dose studies <ul style="list-style-type: none"> ▪ Short term ▪ Sub chronic ▪ Chronic • Reproductive studies <ul style="list-style-type: none"> ▪ Teratogenicity ▪ Fertility ▪ Peri/postnatal • Carcinogenicity • Genotoxicity • Other <ul style="list-style-type: none"> ▪ Mechanistic ▪ Specific organ toxicity ▪ Immunotoxicity ▪ Neurotoxicity ▪ Toxicity of metabolites and impurities ▪ Human toxicological data ▪ Toxicity of mixtures ▪ In-vitro studies
<p>End-use product details</p> <ul style="list-style-type: none"> • Distinguishing trade name • Formulation type • Active constituents and concentration • Formulation composition • Basic physical and chemical properties 	<p>Clinical data</p> <ul style="list-style-type: none"> • Postmarketing reports • Adverse drug reaction reports • Additional clinical reports • Epidemiology studies • Poisoning reports
<p>Physicochemical properties of the active ingredient</p> <ul style="list-style-type: none"> • Structure of the drug or chemical • All relevant chemical and physical properties 	<p>Monitoring for public health impact of rescheduling decision</p>
<p>Pharmacology</p> <ul style="list-style-type: none"> • Structural and pharmacological relationship to other drugs • Pharmacokinetic and pharmacodynamic profiles • Interactions, incompatibilities, side-effects or adverse effects 	<p>Occupational health and safety details (if applicable)</p>
<p>Toxicology</p> <ul style="list-style-type: none"> • Summary of known toxicology of the drug • Summary of known metabolism of the drug • Summary of previous submissions, if applicable • Relevant details of any published and unpublished toxicological investigations of the drug 	<p>Regulatory status in Australia and overseas</p> <ul style="list-style-type: none"> • Approved indications for drugs • Detailed information relating to the classification or regulation of the availability of drug in significant overseas countries (Canada, Sweden, Netherlands, New Zealand, UK & USA)
<p>Statistical analysis</p>	<p>Consumer education programs</p>

Table 6: Steps in the regulatory amendment process to de-schedule drugs to nonprescription status at the federal level in Canada

<p>Step 1: Consultation</p> <ul style="list-style-type: none"> • Draft of Regulatory Impact Assessment Statement (RIAS) • Internal Consultation • Review and analysis of internal comments • External consultation (stakeholders, other manufacturers etc.)
<p>Step 2: Pre-publication in <i>Canada Gazette</i> Part I</p> <ul style="list-style-type: none"> • Review and analysis of external comments • Preparation of full official Part I package for <i>Canada Gazette</i>. This package includes RIAS, approved copies of regulation, memos to the Director General (DG) and the Minister, Communications Plan, letter to the Assistant Clerk of the Privy Council and a prepublication notice • Approval of the proposed regulatory amendment by the DG, Assistant Deputy Minister (ADM), Deputy Minister (DM) and Minister • Approval by SCC • Pre-publication in <i>Canada Gazette</i> Part I • Comment Period
<p>Step 3: Publication in <i>Canada Gazette</i> Part II</p> <ul style="list-style-type: none"> • Review and analysis of stakeholders' comments from Part I • Preparation of a package for publication in <i>Canada Gazette</i> Part II. This package contains the RIAS, stamped copies of the regulation and an order, memos to DG and Minister, letter to the Assistant Clerk of the Privy Council, a recommendation and a communication plan. • Approval by the DG, ADM, DM and Minister • Approval by Special Committee of Council • Registration • Publication in <i>Canada Gazette</i> Part II

Table 7: Summary of data requirements for a reclassification application in The European Union

<p>Safety</p> <ul style="list-style-type: none"> • Summary of animal or human studies showing low general toxicity and no reproductive toxicity, genotoxic, carcinogenic properties with the experience/exposure to the product. • Post-marketing experience in wide ranging patient population under prescription status for preferably five years, or shorter period if active substance has been in use as a foodstuff or as a metabolite of a known active substance. • Adverse reactions information, experience of use without medical supervision from foreign sources, including numbers of patients treated, demographic details, indications for use and dose. • Safety profile summarized as per EU guidelines, to include: <ul style="list-style-type: none"> ▪ Post-marketing surveillance study reports. ▪ Clinical trials and published literature related to safety. ▪ Discussion of reactions arising from misuse and unknown reasons. ▪ Data extrapolation from the prescription use population to nonprescription use population. • Potential and consequences of drug interactions with commonly prescribed drugs. • Consequences of misuse, abuse or overdose. • Consequences of consumer using upon misdiagnosis of symptoms. • Consequences of incorrect or delayed diagnosis of symptoms related to the product.
<p>Efficacy</p> <ul style="list-style-type: none"> • When application includes changes in indications or posology, otherwise not needed. • Justification of a suitable time-period for treatment of the suggested indication(s). • A proposed pack size.
<p>Product information</p> <ul style="list-style-type: none"> • Label and leaflet examined for comprehensive information and effectiveness in protecting consumers from any safety hazards (<i>very important</i>) • Description of use of the product and circumstances when referral for medical advice is appropriate from the label. • Compliance of labels with requirements as per Council Directive 92/27/EEC on the readability of the label and package leaflet. • Contraindications and warnings, such as advice limiting duration of treatment or the need to consult a doctor in certain situations.
<p>Package</p> <ul style="list-style-type: none"> • Discussion of a change of container when applicable together with necessary documentation.

Table 8: Classification of proprietary drugs (nonprescription medicines) in Japan

<i>Category</i>	<i>Description</i>
Class 1	Drugs which contain active ingredients which have been used neither in prescription nor in OTCs (referred to as "New active ingredients")
Class 2	Drugs which contain active ingredients, other than "New active ingredients", which have not been used as active ingredients in already approved OTCs (referred to as "New non- prescription ingredients")
Class 3	Drugs which consist of active ingredients which have been used in already approved OTCs but which have not been used in the therapeutic category in question (referred to as "Newly combined ingredients"), and drugs which are different from already approved OTCs in the therapeutic category in question in terms of combinations of active ingredients, or indications and effects, or administration and dosage. (However, drugs in either Classification 4 or 5 and drugs which comply with Approval Standards shall be excluded.)
Class 4	<p>After completion of Post Marketing Surveillance on safety during use of drugs in any one of Classifications, 1, 2, and 3 (collectively hereinafter referred to as "New non-prescription medicines"), drugs which are applied for approval as drugs containing either "New active ingredients" or "New non-prescription ingredients" or "Newly combined ingredients" but which have differences in combination of active ingredients used in already approved OTCs. The differences correspond to the following two cases. However, these drugs shall be limited to those with the same administration and dose, and indications and effects as already approved OTCs, and with the same or slightly different dose forms from already approved OTCs.</p> <p>(1) When only active ingredients with pharmacological actions different from those of "New active ingredients", "New non- prescription ingredients" or "Newly combined ingredients" are different.</p> <p>(2) Where ingredients with different pharmacological actions in the case (1) have mild actions with no direct relations to therapeutic efficacy.</p>
Class 5	Drugs which belong to the therapeutic categories with the Approval Standards and only whose dose forms are different from those specified in the Approval Standards, and drugs which belong to the therapeutic categories without the Approval Standards and only whose dose forms are different from those of the already approved OTCs in the therapeutic categories in question (Limited to those with special dose forms).
Class 6	Drugs which conform to the Approval Standards, or drugs which do not fall into any one of the Classifications 1 through 5 above.

Table 9: Data required for approval of nonprescription drugs in Japan

Data required	Class of Drugs						
	1	2	3	4		5	6
				a	b		
A. Data on origin and use in foreign countries							
1. Product origin and details of discovery	o	o	o	o	o	o	x
2. Use in foreign countries	o	o	o	o	o	o	x
3. Product profile and comparison with other drugs	o	o	o	o	o	o	x
B. Data on physical and chemical properties							
1. Determination of chemical structure	o	x	x	x	x	x	x
2. Physical and chemical properties	o	x	x	x	x	x	x
3. Specifications and testing methods	o	o	o	o	o	o	o
C. Data on stability							
1. Long-term storage test	o	x	x	x	x	x	x
2. Severe test	o	x	x	x	x	x	x
3. Acceleration test	x	o	o	o	o	o	o
D. Data on toxicity							
1. Acute toxicity	o	#	#	x	x	x	x
2. Subacute toxicity	o	#	#	x	x	x	x
3. Chronic toxicity	o	x	x	x	x	x	x
4. Effects on reproduction	o	x	x	x	x	x	x
5. Dependence	#	x	x	x	x	x	x
6. Antigenicity	#	#	x	x	x	x	x
7. Mutagenicity	#	x	x	x	x	x	x
8. Carcinogenicity	#	x	x	x	x	x	x
9. Local irritation	#	#	#	x	x	x	x
E. Data on pharmacological action							
1. Test supporting effectiveness	o	x	x	x	x	x	x
2. General pharmacology	o	x	x	x	x	x	x
F. Data on ADME							
1. Absorption	o	#	#	x	x	#	x
2. Distribution	o	x	x	x	x	x	x
3. Metabolism	o	x	x	x	x	x	x
4. Excretion	o	#	#	x	x	#	x
5. Bioequivalence	x	x	x	x	x	x	x
G. Data on results of clinical trials							

Key to symbols: o=Required #=Depending on the case x=Not required

Table 10: Description of clinical trial requirements for nonprescription medicines in Japan

<i>Class</i>	<i>Description</i>
Class 1	Clinical trials need to be conducted at more than five medical institutions with more than 150 patients
Class 2	Clinical trials need to be conducted at more than five medical institutions with more than 150 patients Note: Clinical data may be reduced to three medical institutions with 60 patients for those Rx-to-OTC switch drugs whose safety and efficacy profile for general use has been well demonstrated by clinical investigations or post-market surveillance previously conducted.
Class 3	Clinical trials need to be conducted at more than three medical institutions with more than 60 patients
Class 4a	Clinical trials may need to be conducted at more than two medical institutions with more than 40 patients

MANUSCRIPT III

OTC SWITCH CASE HISTORY EVALUATION: NICORETTE®

Abstract

As part of the FDA's current review of its regulatory approach to nonprescription medicines, it is necessary for stakeholders to contribute to the ongoing discourse. Reclassification of prescription medicines to over-the-counter status is an important topic attracting the attention of many in the United States and elsewhere. This article presents a detailed examination of FDA's application of switch regulatory policy, the use of innovative consumer communication and education tools in the OTC environment and overall public health impact of the switch using the Nicorette case as an example. Post switch evidence shows that OTC reclassification of Nicorette achieved the anticipated goal of balancing increased access with decreased control in the OTC atmosphere resulting in a positive public health outcome in the area of smoking control.

Introduction

The US Food and Drug Administration (FDA) is currently conducting a comprehensive review of its regulation of nonprescription medicines and has asked for public comment (1). Hence, interested professionals are closely scrutinizing the FDA's application of regulatory policy for reclassification of prescription medicines to over-the-counter (OTC) status. Accordingly, to appraise a recent and successful OTC switch from the perspectives of the regulatory basis and public health impact, the case of Nicorette[®] is useful. The switch of Nicorette[®] chewing gum, a smoking cessation aid, to OTC status by the FDA in 1996 is a unique and important example. This switch is very important as it resulted in the availability of the first smoking cessation aid available without a prescription for adults in battling nicotine addiction.

Within the context of studying the application of regulatory policy by the US FDA in rendering switch decisions, this case is rather exclusive. The Federal Food, Drug & Cosmetic Act requires that prescription control be applied to habit-forming drugs as per Sec.503(b)(1). As the addictive properties of nicotine are widely documented and acknowledged, the switch of Nicorette (that contains nicotine as active ingredient) to OTC status is remarkable (2). Nicorette is distinctive among OTC medicines, as it is part of a larger behavioral program that emphasizes individual commitment to achieve smoking cessation. The concomitant tools used for effective consumer communication employed by the sponsor in this case are also matchless within the OTC medicines arena. For these reasons the OTC switch of Nicorette is worthy of detailed examination.

Background

Nicotine is a ganglionic cholinergic-receptor agonist (2,3). The pharmacologic actions of nicotine are complex and include a variety of effects mediated by stereospecific binding to receptors in autonomic ganglia, the adrenal medulla, the neuromuscular junction, and the brain. Nicotine exhibits both stimulant and depressant effects in the peripheral and central nervous systems. The principal pharmacologic effect of small doses of nicotine is initial, transient stimulation of autonomic ganglia; large doses or prolonged neuronal receptor exposure to nicotine results in subsequent persistent depression of receptor activity. Nicotine produces marked CNS and respiratory stimulation. The cardiovascular effects of nicotine generally are dose dependent and are mediated principally via stimulation of sympathetic ganglia and the adrenal medulla. Chronic use of nicotine may result in psychologic and physical dependence, and tolerance to some of the pharmacologic effects may occur. As adjuncts in the cessation of cigarette smoking, nicotine polacrilex and transdermal systems of nicotine provide alternative sources of nicotine that help reduce the withdrawal symptoms associated with nicotine dependence.

The FDA in January-1984 and June-1992 approved Nicorette 2mg and Nicorette 4mg respectively. In December-1994, the sponsor submitted a supplement to the new drug application (sNDA) to switch Nicorette from prescription to OTC status. A summary of the proposed Nicorette OTC product is presented in table 1. The proposed OTC doses and label indications were same as those for the approved prescription product. At the time of switch application, Nicorette was available as a

prescription product in over 50 countries and as a nonprescription product in over 30 countries.

On 28 September-1995, the Nonprescription Drug and Drug Abuse Advisory Committees to the US FDA met jointly to consider the OTC switch application for Nicorette®. Present on behalf of the Drug Abuse Advisory Committee (DAAC) were four members and a consumer representative. The Nonprescription Drug Advisory Committee (NDAC) consisted of seven members, one guest member and a representative each from the industry and consumers. An analysis of the deliberations that took place at this meeting (4) is presented in the subsequent sections. The objectives are to expound the application of the OTC switch regulatory policy, evaluate the regulatory options in rendering the switch decision by the Advisory Committees and examine the public health consequences of this switch decision.

Open hearing

During the public comment section, Thomas Cooper, D.D.S., C. Everett Koop, M.D., Alfred Munzer, M.D. and Rev. Herbert Watson Jr., stated their opinions on this matter. Dr. Everett Koop, former Surgeon General speaking on his own as a physician and private citizen supported the switch of nicotine gum from prescription to OTC use. He said, *"I believe one important answer is to make treatments that have been proven to be safe and effective in the prescription setting more widely available by shifting them to OTC availability. I believe nicotine gum is one of those treatments and I urge to consider this switch application favorably. Smokers do want help. And everything that we can do safely and prudently to get them that help will speed the day when we will truly have a smoke-free society"*. Dr. Thomas Cooper, a dentist, retired professor,

smoking-cessation researcher and a smoker for 36 years gave personal testimony on the effectiveness of Nicorette in helping him quit nicotine addiction. He also endorsed the safety of nicotine gum based on data observed from first hand experience as a researcher in the area of smoking control. He urged that easily understood directions for proper use are essential and that the benefits of OTC availability of nicotine gum are far greater than the risks. Dr Munzer, Co-Director of the Department of Pulmonary Medicine at the Washington Adventist Hospital and a past president of the American Lung Association said that the reasons for making nicotine replacement therapy available OTC are its safety, effectiveness and lack of significant interactions with other medications. He added that the most important reason is, *"because it answers a major public health need"*.

Rev. Herbert Watson, Jr., a pastor in East Baltimore and the board chairperson for a program called Heart, Body, and Soul, a cooperative partnership between CURE, a ministerial group in East Baltimore and the Johns Hopkins Center for Health Promotion, who was instrumental in developing a church based smoking cessation program stated his concern about the restrained access for nicotine gum within the prescription setting. He emphasized the need for free and convenient access to nicotine gum, not only in medically underserved communities, but also across the entire nation. He encouraged the panel to make nicotine gum easily available to communities and individuals who can use it safely and effectively.

Sponsor presentation

The sponsor's presentation to assist the advisory committees in assessing the risks and benefits and demonstrate the validity of Nicorette OTC switch can be broadly

divided into five parts. An overview of the entire structure of the presentation was followed by the epidemiology and treatment of smoking, results of prescription-to-OTC switch development program for Nicorette and how they satisfy FDA's switch requirements for safety and efficacy, risk-benefit analysis of Nicorette in terms of dependence potential, abuse and misuse liability, and, marketing plan for Nicorette, accompanying behavioral materials including development of the label for Nicorette and how it satisfies the switch requirements for patients to self-select. The types of studies conducted and results presented by the sponsor to elucidate each of the aforementioned aspects have been tabulated in table 2. Information pertaining only to the unique aspects of Nicorette in the context of OTC switches will be elaborated.

As the proposed OTC product was at the same doses and for the same indication as the prescription product and as enormous post-marketing safety data in prescription and OTC settings in a variety of regulatory environments was available, proving the safety and efficacy for Nicorette 2mg and 4mg in the OTC setting was relatively simple. The sponsor demonstrated the safety and efficacy by conducting multi-center, simulated OTC actual use studies to replicate the absence of physician intervention. The two most remarkable aspects of this OTC switch case are demonstration of an acceptable risk in terms of dependence potential, abuse and misuse liability and the development of labeling material and consumer communication tools that facilitate effective self-selection in the uncontrolled OTC atmosphere.

The sponsor addressed the issue of long-term dependence by arguing that mere long-term use of a medication does not indicate dependence. Additionally, long-term use must be characterized by compulsive use and impaired control, i.e. the drug

comes to control your behavior. So long-term use in and of itself does not necessarily mean dependence. Results from the meta-analysis of all the clinical trials that reported long-term use showed that 18% of users still used the gum at the end of six months and this statistic decreased to about one percent in two years. Among the special subgroup of people who quit smoking by using the gum, the percentage using the gum at end of six months was 35% and decreased to 3% in two years. Clearly, there was longer than directed use observed in all the clinical trials. The reasons that the sponsor listed to contend that these results do not represent long-term dependence were as follows:

- (1) In the clinical trials, the nicotine gum was provided free of cost. A study where people were randomly assigned to differently priced nicotine gum showed that the simple intervention of having to pay for the gum decreased long-term use by two thirds.
- (2) Similar users of cocaine and cigarettes upon absence of any intervention showed a very small decrease in the proportion of users over a two-year period, relative to the fall to 3% with the nicotine gum.
- (3) Further, there was no dose escalation observed among the long-term users with the nicotine gum. Also, simple reassurance and education of long-term users was adequate to wean them off the nicotine gum.
- (4) The observed long-term use may be attributed to the fear of falling back into the smoking habit having once quit smoking with the nicotine gum and residual craving for nicotine upon smoking cessation that takes a long time to be weaned off completely.

The sponsor contended that the abuse liability associated with Nicorette was minimal and acceptable. They asserted that in the context of abuse liability, more important than the chemical effects of the drug is the drug delivery device. Upon cigarette smoking, nicotine enters the arterial circulation from the pulmonary circulation and goes straight to the brain without being diluted with the venous blood leading to high nicotine concentrations. With the gum, nicotine is absorbed through the buccal membrane and is diluted with the venous blood before entering the brain. Also, inhaling the drug is the fastest way to get it to the brain. Hence, the addiction to nicotine via cigarettes is due to the very rapid onset of the effect. The sponsor argued that the addiction to nicotine via cigarettes is due to the high arterial concentrations, the rapid time to reach the brain, the frequency of use and not due to the chemical per se. Also, when the dose of nicotine (as cigarettes) was increased and the users were asked to rate their liking for nicotine, the liking increased with the dose. With the gum, the response of the users was the opposite as craving for nicotine decreased with higher dose. The differences in the responses between cigarettes and gum were attributed to the different pharmacokinetic characteristics. The potential for abuse by young adults was countered based on the following:

- (1) Nicotine chewing gum is difficult to chew and does not taste good (but is palatable).
- (2) Drug use among teenagers generally is initiated due to peer-pressure, rebelliousness and anti-authoritarianism. Chewing gum is not considered "cool" and does not conform to the badge behavior of being "cool" as is the case with

alcohol or cigarettes. Also, increased doses with the nicotine chewing gum do not lead to faster onset of action, but only increased nausea.

Based on this rationale of the benefits arising from increased access, especially for young adults and medically underserved, and the minimal risks of long-term dependence and abuse liability due to the benign pharmacokinetics of the nicotine chewing gum, the sponsor urged the Advisory Committees to favorably consider their OTC switch application.

The labeling for OTC Nicorette was developed based on labeling comprehension studies and was suitable for sixth to seventh grade reading comprehension levels. The marketing plan and associated consumer communication methods proposed for OTC Nicorette were exceptional by any measure. The sponsor claimed that its objective is to help Americans quit smoking and become Nicotine free. Their two-fold strategy was to very carefully manage the expectations for the OTC product and develop a marketing plan to balance control with the greater access of the OTC product. The Nicorette target consumer was that smoker who has successfully crossed the stages of thinking about quitting, firming up their determination to quit and is ready to take action. The sponsor termed such smokers as "Committed Quitters" and did not wish to speak to smokers in the evolutionary stages before the committed quitter stage in their programs and marketing. The sponsor's advertising plan positioned OTC Nicorette as an aid that can help quit smoking as opposed to a magic bullet. Further, Nicorette OTC product was only one part of the complete package that would consist of a user's guide, an audiotape and a number of program elements that are motivational and can influence the individual's behavioral patterns and ability to successfully quit.

The sponsor developed a program called the Committed Quitters (CQ) program. The program becomes apparent immediately upon opening the package and contains an 800 number encouraging the individual to call and enroll in a support program. Upon calling the 800 number, the individual is interviewed to clarify the reasons for their decision to quit and informed of the barriers they need to overcome to successfully quit. Subsequently, a personalized user's guide calendar is put together for the individual with the reasons driving their decision to quit and the barriers they could not overcome in the past. Following initial enrollment in the CQ program, there are about five interventions to help keep the individual from relapsing into smoking. If the individual was chewing too many pieces of gum than recommended, there were also programs that assisted them to wean off the gum, another 800 number is provided to call and talk to a counselor who can assist the individual in weaning off the gum or who has relapsed into smoking. The CQ program of which Nicorette OTC product was only one part, was an active and interactive program for not only helping individuals as a behavioral program but also assist those who have relapsed to smoking.

In terms of merchandising activities, the product would be priced above the impulse level, it would not be sold in vending machines, no free samples would be distributed even to physicians, it would be part of a theft deterrence program and would be sold only to individuals above over 18 years of age. The sponsor also declared that they were working with many insurance companies to urge them to cover this OTC product and said that most insurers agreed to do so. In terms of cultural barriers, stores in predominantly Spanish speaking communities would be provided with special 800 numbers and all the educational material would be in Spanish. As the proposed OTC

product was relatively expensive, the sponsor had convened an independent advisory panel to propose strategies for developing an outreach program for the medically underserved areas and increasing their access to OTC Nicorette. The sponsor also proposed the use of an exhaustive post-marketing surveillance program for OTC Nicorette. As detailed here, the sponsor developed a comprehensive behavioral program, pioneered the use of communication tools such as toll free numbers, audio tapes and counselors to achieve effective consumer education, voluntarily committed to numerous restrictions, clearly defined their target consumer and market positioning of the OTC product, addressed the special needs of medically under served and ethnically diverse communities and proposed a comprehensive post-marketing surveillance program to balance control and increased access within the OTC setting. An examination of the OTC medicines arena will clearly distinguish these aspects of OTC Nicorette making it a unique and exclusive OTC switch.

FDA presentation

FDA focused on the methodology and results from labeling studies submitted by the sponsor. The main concerns expressed in this area were:

- (1) The sponsor conducted labeling studies based on the assumption that the intent to heed (observing the directions) the label was a direct indicator of comprehension (obeying the directions) when compared with the same for an existing OTC product (as control). This assumption was not justified based on results presented for self-selection of right dose (based on number of cigarettes smoked), the decision not to use Nicorette by patients who had cardiovascular

conditions or were pregnant, as subjects understood the label directions but did not obey them.

- (2) During the process of refining the label content, evaluative questions for the subjects were phrased and iterated in such a manner to inevitably lead to the desired response. Also, details of demographics were not presented to understand the nature of the subject population. Questioning was leading and did not delve into the attitudes and motivations that affect the actual behavior.
- (3) Study methodology and design of questionnaire make it difficult to rely on the results. They do not demonstrate with reasonable confidence that patients who are directed to see a doctor first may do so at a high rate despite the warnings.

The following were comments on the results from two quit rate studies in the prescription setting.

- (1) Participants in clinical trials such as those for the NDA are different from consumers in the general OTC population and quit rates may not be representative of the actual results that may be expected in an OTC setting.
- (2) The demographic distribution of the study samples also may not be as representative of the smoking population who may elect to use the OTC smoking cessation product.

Commenting on the issue of abuse and dependence, the FDA reviewer summarized that most long-term use is seen in quitters than in non-quitters, who represent the positive outcome. Continued use declines for Nicorette gum generally after six months to one year and there are very few reports at two years.

Regulatory options

FDA informed the committees and the sponsor that to approve an OTC switch, it is essential that the following two conditions be met:

- (1) The product is safe and effective under conditions of self-medication when used as directed in the proposed label.
- (2) The availability of the product in the OTC environment is of acceptable risk.

Additionally, the law states in this context that neither the toxicity of the drug, the method of use, or any other potential harmful effect of the product necessitate that the product remain prescription only.

These conditions offered the committees the criterion by which they were to judge the suitability of Nicorette as an OTC medicine under the sponsor's plan. The FDA officer stated that the Agency received numerous requests to address the issue of pediatric access to therapeutic OTC nicotine upon publication of this meeting in the Federal Register. The committees were requested to phrase their recommendations solely in terms of what the Agency should accomplish. The committees were asked to describe their recommendations in terms of the objective to be reached and not in terms of specific means of accomplishment. Also, any recommendation to restrict the OTC access to Nicorette will have to be subject to careful review and potential modification by the Agency. The list of specific questions related to the proposed Nicorette OTC switch, upon which the committees had to vote was also made available for discussion. This list of questions is presented in table 3.

Committee discussion

Over the topic of safety and efficacy, concern was expressed on adverse effects related to Nicorette use in conjunction with smoking. The clinical data from OTC use trials, original submission and post-marketing surveillance showed that Nicorette was frequently used in combination with smoking, but there was no evidence of any undue risk associated with this behavior. Also, it was suggested that the labeling for both proposed OTC doses be indistinguishable and must reinforce the augmented success with participation in a full behavioral/support program as opposed to just chewing the gum. The sponsor was asked if there was a recommended time at which users should restart the program, if they were not successful in quitting on first attempt. The sponsor replied that there was no such recommendation being made. The issue of the product being efficacious for adolescents (12 to 18 years) if purchased by a responsible party and used under their supervision and pregnant women was raised. The sponsor responded that while their clinical trials do not support any such conclusions, there was empirical evidence that the product was effective in adolescents and a better alternative than cigarettes for pregnant women. There was strong consensus that the efficacy in the 12 to 18 year population needed to be studied. The committees' vote on safety and efficacy of Nicorette in the OTC environment was unanimous in consent.

On question two (need for learned intermediary in special populations) posed to the committees, it was concluded that adolescents, pregnant women and individuals with coronary artery disease might require special physician intervention. During discussion a committee member raised the consequences of making the product OTC in terms of reimbursement. Specifically, the committees were concerned that the access to

the OTC product may be diminished due to lack of reimbursement if the prescription product is eliminated. Under present law, it is not possible to classify the same product for the same indications at the same dose simultaneously as OTC and prescription products. Hence, the FDA was urged to retain both prescription and OTC classifications. Also, the sponsor reassured that they would be working with managed care organizations to make the coverage universal and they were in the process of developing a pilot program to identify strategies that would help increase affordability of the product especially to medically under served and poor section parts of our population. The committees did not express any apprehension for misuse or abuse with the exception of individuals chewing the gum longer than directed. However, that was considered a positive cost benefit ratio provided the total tobacco consumption is cut down. Also, the Canadian experience with the 2mg product, where it was OTC since 1993, reinforced the consensus that there was no serious risk of abuse.

Addressing the issue of special protection against abuse by children, the committee strongly recommended the need for the Agency to take active steps in examining the usefulness of nicotine replacement therapies in populations that are beginning to use tobacco. The committees did not regard children as a potential source of abuse for this product, but they were very concerned that the product was not designed to assist children in smoking cessation due to lack of studies and urged the FDA to devise solutions for this problem. The question related to efficacy claim based on numerical quit rates is specific to the Nicorette case as the medication is part of a larger behavioral program. Further, depending on the patients and the kind of concomitant behavioral therapy they received, the quit rates vary from less than one

percent to over eighty percent. In order to manage the consumer expectations within a clinically realistic domain and prevent a numbers war between sponsors based on claims of effectiveness, this question was posed to the committees. The committees strongly endorsed phraseology that would positively reinforce the consumer's determination to quit without exaggerating the level of success. They urged that that label refrain from any numerical characterization of quit rates and emphasize relief from withdrawal symptoms (to assist in quitting) and participation in a concomitant behavioral program.

An additional question that was also discussed by the committees was on the subject of warnings related to concomitant medications. Specifically the question was, is there a need to have specific warnings about theophylline and antidepressants or is a general warning about prescriptive medications adequate? On this question the committees arrived at the consensus that warnings on the label be general and broad in nature against all prescription medicines and suggested that the label be subject for review and change if evidence is found that such an action is necessary.

Post committee meeting

Based on the recommendations of the joint advisory panel, FDA approved OTC status for Nicorette in both 2mg and 4mg strengths on 12 February-1996. In a related talk paper, FDA stated that almost half of those who use Nicorette are able to stop smoking for at least a few days, but many start smoking again. FDA also said that most smokers must try to quit several times before they completely stop. Evidence also suggests that the OTC availability of Nicorette led to an overall positive public health impact by promoting cessation. A report published by the Center for Disease Control

and Prevention in 1997 concluded that the OTC availability of nicotine medications encouraged smoking cessation activity (5). Additionally, results of a study evaluating the use of FDA approved pharmacologic treatments for tobacco dependence in the United States between 1984 and 1998 published in 2000 indicated that the availability of OTC products increased pharmacologically assisted quit attempts (6). The estimated number of quit attempts ranging from 2 to 3 million during 1993-1995 increased to approximately 6 million in 1996, coinciding with the availability of nicotine gum as an OTC product. Also, the number of average monthly estimated quit attempts was 642,000 during May 1996-May 1997 when nicotine gum became available OTC, compared with 259,000 during January 1993-April 1996.

Conclusion

This OTC switch demonstrates that the sponsor employed innovative consumer education and communication tools, pioneered the development of concomitant behavioral support programs and emphasized the enormous public health benefit of OTC Nicorette in successfully obtaining OTC status for a habit forming drug substance. Post switch evidence shows that OTC reclassification of Nicorette achieved the anticipated goal of balancing increased access with decreased control in the OTC atmosphere. It may be concluded that sponsors of OTC switch applications must devise creative methods to balance the risk associated with increased access in an OTC environment to maximize the overall public health benefit and effectively switch prescription drugs to OTC status.

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Table 1: Description of proposed OTC Nicorette® product

Name	Nicorette®-chewing gum formulation
Active ingredient	Nicotine from nicotine polacrilex
Dose	2mg for smokers under 25 cigarettes a day and 4mg for smokers over 24 cigarettes a day
Action	Stop smoking aid
Use	To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking
Program	<p>Committed Quitters program:</p> <ul style="list-style-type: none"> • Six month duration • Toll free numbers for behavioral support and counseling • User's guide, audio tape and calendars • Starter kit of 108 pieces for 12 weeks, followed by refill pack of 48 pieces • Emphasizes the importance of "individual commitment" in successful quitting • Manages consumer expectations in a realistic manner
Restrictions	<ul style="list-style-type: none"> • Not for sale to those under 18 years of age • Proof of age required • Not to be sold in vending machines

Table 2: Summary of types of studies and information presented by the sponsor

<p>Epidemiology, treatment and behavior associated with smoking</p> <ul style="list-style-type: none"> • Mortality due to cigarette smoking and public health significance • Initiation of teenage smoking and difficulty in quitting without treatment • Rationale for nicotine replacement in smoking cessation • Effectiveness and success of nicotine replacement in conjunction with behavioral support in smoking cessation • Evidence demonstrating smoker attitudes favoring "free access" in smoking cessation
<p>Safety and efficacy of Nicorette in the OTC environment</p> <ul style="list-style-type: none"> • Two 12 week long studies conducted to prove safety and efficacy in an OTC setting • One follow-up study to the above two studies was conducted at 6 and 12 month intervals upon initiation of treatment to evaluate extensive treatment • Two studies were conducted to evaluate effectiveness in the prescription setting • Post-marketing safety data collected since the initial marketing of Nicorette
<p>Risk-benefit assessment of making Nicorette available OTC</p> <ul style="list-style-type: none"> • Higher cessation rates due to OTC availability of Nicorette • Prevention of tobacco related mortality due to OTC status • Dependence, abuse liability and misuse data from several sources
<p>Development of labeling</p> <ul style="list-style-type: none"> • Label comprehension studies • Additional components of marketing plan • Behavioral support and program

Table 3: List of questions presented to the Advisory Committees for voting by the FDA
in relation to the proposed Nicorette OTC switch

Number	Question
1	Is there evidence to demonstrate that the product is safe and effective through self-medication, when used as directed? This question was posed for both the proposed 2mg and 4 mg OTC doses.
2	Are there some consumers who should use this product under the direction of the physician or under the supervision of a physician?
3	Is there a risk of misuse or abuse of this product in the OTC environment?
4	Should the Agency take appropriate measures to protect the misuse or abuse of this product by children and adolescents?
5	Should the sponsor's efficacy claim be based on numerical quit rate or a general statement indicating that the product is effective in relieving withdrawal symptoms and of benefit in smoking cessation?

MANUSCRIPT IV

OTC SWITCH CASE HISTORY EVALUATION: METAPROTERENOL

Abstract

Globally, due to increasing use of nonprescription medicines, the associated regulatory aspects are receiving close attention and scrutiny. The US Food and Drug Administration (FDA) is presently conducting a comprehensive review of its regulatory approach to nonprescription medicines. The FDA has asked if the Agency should itself initiate prescription to over-the-counter switches. A response is presented through the analysis of FDA's unsuccessful attempt, upon its own initiative, to switch metaproterenol sulfate and the lessons derived from this unique switch case. Also, certain important switch issues scheduled to be debated at an unprecedented joint advisory committee meeting convened to consider a citizen switch petition in May 2001, are addressed in this article. It is concluded that FDA is encouraged to initiate switch proposals, but refrain from doing so unilaterally, and properly manage the process of considering its switch proposals to ensure active participation of all stakeholders.

Introduction

Growing global interest in self-medication and related economic benefits accentuate the importance of and necessity for a regulatory framework developed on the basis of sound scientific principles. The US Food and Drug Administration (FDA) recently announced a public hearing to evaluate the Agency's approach to regulating over-the-counter (OTC) drug products (1). The purpose of the hearing was to solicit information from, and the views of, interested persons, including scientists, professional groups, and consumers. One specific question that the Agency posed in this context is: *should FDA be more active in initiating switches of prescription products to OTC use?*

In the development of an objective response to this question, it is helpful to review and evaluate the well-known incident of the metaproterenol switch, when FDA upon its own initiative allowed OTC marketing of metaproterenol and later had to rescind on its decision. In the historical context of examining the application of FDA's OTC switch policy, the metaproterenol case is unique and offers important lessons. Hence, a detailed examination of the metaproterenol case history is of enormous instructional value.

Background

In 1972, FDA initiated OTC drug review and rulemaking as to the classification of OTC products as safe, effective and not misbranded. Initially, FDA established an advisory panel for each of the twenty-six OTC therapeutic categories. After each advisory panel completed its work, FDA published its *Report and Proposed Monograph*, allowing a ninety-day comment period. After reviewing these comments FDA published a tentative final monograph (TFM), allowing an additional thirty-day

period for comments or request for oral hearing before the Commissioner, after which it published a *Final Monograph (FM)* for the particular OTC product class.

Metaproterenol was first approved for marketing as a prescription bronchodilator under an NDA in 1973. As part of the OTC review, the Advisory Panel on OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products presented its report to the FDA that was published in 1976 (2). This panel's report did not contain any discussion pertaining to metaproterenol as no one presented any data or information for its OTC use.

In October-1982 the FDA issued a notice of proposed rulemaking in the form of a TFM for OTC bronchodilator drug products (3). In this TFM, FDA on its own initiative included metaproterenol sulfate as eligible for OTC use although the advisory panel had not examined its suitability for OTC use. As per the prevailing enforcement policy mechanism, two pharmaceutical manufacturers began interim OTC marketing of metaproterenol upon publication of the TFM and while awaiting the final monograph.

The controversy

Shortly after the OTC marketing of metaproterenol began, FDA started receiving the first of many letters questioning the Agency's decision to allow metaproterenol to be marketed OTC. The letters criticized, the decision to allow OTC marketing, not notifying the professional community in advance and the Agency's failure to await comment, or seek the advice of its Pulmonary-Allergy Drugs Advisory Committee (PADAC).

Specifically, some of the critical comments received by the FDA were:

1. Recognized experts in the area of allergy treatment either disagreed or were divided in opinion over the safety of metaproterenol under OTC conditions.
2. Pediatricians expressed concern over the potential misuse of OTC metaproterenol by children. Potential for misuse of OTC metaproterenol by asthmatics seeking more relief by exceeding the dose instructions on the OTC label.
3. As metaproterenol has a longer elimination half-life than epinephrine (another drug used for similar conditions and was available OTC for a long time) the drug could mask the symptoms of a serious asthma attack deterring persons in need of immediate medical attention.
4. As metaproterenol had a longer onset of action, patients may overuse than the recommended dosage under the mistaken belief that they are not obtaining the expected relief at the suggested dosage.
5. There was unsatisfactory experience with OTC metaproterenol in other countries. Although the drug remained OTC in some countries, Great Britain had reverted the OTC status of metaproterenol sulfate inhalers and other similar aerosol bronchodilators containing isoproterenol to prescription status on the basis of misuse or improper use of such products that led to increased mortality among asthmatics in the mid 1960s.

Resolution of controversy

In response to these criticisms, FDA arranged a meeting of its PADAC to discuss the OTC status for metaproterenol. After the PADAC heard presentations from the proponents, principal critics, FDA staff and the manufacturers who were marketing

OTC metaproterenol on an interim basis, and based on its own deliberations, the committee recommended to FDA that it rescind its decision to permit OTC marketing of metaproterenol by a vote of 4 to 3.

FDA response

Following the recommendation of its PADAC, FDA published in the Federal Register on 3 June-1983 that it has concluded that it should accept the advisory committee's recommendation (4). FDA stated that it reached such conclusion based on:

1. Reservations within the medical community about whether metaproterenol sulfate metered dose inhalers can be safely marketed without the safeguard of a prescription limitation and professional supervision of the drug's use in asthmatics. FDA intended to more fully consider such reservations before it could allow metaproterenol to be marketed OTC.
2. The procedure by which metaproterenol was permitted to enter the marketplace as an OTC product led to unintended confusion and controversy that, if allowed to continue may, disrupt the relationship between physicians and their patients and produce unnecessary anxiety among asthma sufferers seeking relief from their symptoms through OTC therapy.

In order to further clarify the Agency's positions on this matter, FDA elaborated its opinion on the safety of OTC metaproterenol and the regulatory mechanism by which it was switched. FDA stated that the decision to switch metaproterenol to OTC status was made in the context of an OTC bronchodilator market in which the only metered dose inhaler products available were epinephrine preparations that the Agency believed to be no safer or less effective than metaproterenol sulfate. FDA asserted that despite the

advisory committee's recommendation to rescind, it continued to believe that a careful weighing of the risks and benefits supports the proposal that metaproterenol sulfate should be made available without prescription. On the concern that patients may not follow carefully the label directions, FDA believed that asthmatic sufferers are capable of understanding and heeding instructions for safe use of OTC metaproterenol. In relation to potential for abuse by children, the Agency thought that essentially the same potential existed for children using the product without parental supervision whether the product was sold on prescription or OTC. Nevertheless, the Agency was committed to respect the judgment of the specialists in the field who believed OTC metaproterenol posed a public health risk and consequently decided to disallow the OTC marketing of metaproterenol sulfate metered dose inhalers until the safety issues were resolved.

The Agency also explained its interpretation of the regulatory mechanism based on which OTC sale of metaproterenol was allowed. The enforcement policy to include an opportunity for FDA review for prescription to OTC switches before they occurred was issued in 1975 and codified as 21 CFR 330.13 after allowing public comment. The enforcement policy was later amended in 1982 (47 *Federal Register*, 17738, 23 April 1982) to permit a prescription drug to be marketed OTC if the drug is classified by an OTC advisory panel in Category I (category of drugs that were found to be suitable for OTC use as per the OTC Drug Review process). Also, a prescription drug may be marketed OTC if FDA subsequently concludes that a drug not classified by an advisory panel in Category I later tentatively qualifies for classification in Category I and so states in a Federal Register announcement.

FDA stated that the enforcement policy of 21 CFR 330.13 describes both a general principle and a specific procedure. The specific procedure relates to drugs originally considered by an advisory review panel. The general principle is that a prescription product can be marketed OTC if it is included in the OTC Drug Review and FDA tentatively concludes that it qualifies for Category I. The Agency reasoned that it allowed interim marketing of OTC metaproterenol based on the general principle underlying the enforcement policy of 21 CFR 330.13, although an advisory panel did not consider this drug in its deliberation. In retrospect, due to the enormous public criticism that this switch decision generated, the Agency conceded *"the use of the enforcement policy to allow interim marketing of metaproterenol sulfate metered dose inhaler was inappropriate"*.

Discussion

Based on the metaproterenol experience, it is possible to respond to FDA's question stated at the outset of this article. This discussion of what FDA's regulatory policy should be, on switching prescription products to OTC status, unilaterally, without the support of sponsors is very timely, as FDA has decided to bring a citizen petition seeking OTC status before a joint meeting of its advisory committees. The Agency's PADAC and Nonprescription Drugs Advisory Committee (NDAC) met in an open public hearing on 11 May, 2001 to consider a citizen petition submitted to request the switch of fexofenadine hydrochloride, loratadine and cetirizine hydrochloride (three low and non-sedating antihistamine drugs) to OTC status (5). This response also addresses some important questions to be debated at this *"unprecedented"* joint advisory committee meeting (6).

Under the current regulatory framework the FDA can initiate a prescription to OTC switch based on two separate mechanisms, 21 CFR 330.13 which is part of the OTC monograph procedures or 21 CFR 310.200 known as the switch regulation. Although, the metaproterenol case was not based on the switch regulation (21 CFR 310.200) the key instructional principles from this controversy may be applicable to both circumstances.

From the metaproterenol case, it is abundantly clear that the primary cause for controversy was the lack of adequate notice and opportunity for comment, to all interested parties that would be affected by the switch proposal. It is informative to note that although FDA published its proposal to switch metaproterenol to OTC status as a TFM in the Federal Register, the Agency did not receive much comment on this matter except for two manufacturers who stated their intention to market this OTC product. However, the criticism against the switch proposal mounted rapidly once the interim OTC marketing of the product began. This clearly demonstrates that the proposed rulemaking published in the Federal Register as a TFM failed to reach to all stakeholders interested in this switch proposal. It may be reasoned that a forum such as a public advisory panel review meeting would have been more successful in facilitating effective participation from all interested stakeholders. In fact, FDA's statements in explaining its actions buttress this reasoning. The Agency stated that, *"Not only would the panel's deliberation afford notice that a "switch" of an ingredient was under consideration but those who might object to the switch could convey their concerns to the panel. Finally, any prescription drug converted to OTC status after initial consideration by an advisory panel was necessarily reviewed by outside experts (i.e.,*

the panel members), in addition to medical staff, before any conversion was allowed to take place".

Based on, the growing societal preferences for self-medication, the experiences with medically safe and economically beneficial practice of responsible self-medication since the OTC Drug Review and the learning from the metaproterenol case, the FDA is encouraged to initiate switch proposals that it considers to be safe and effective in an OTC environment and offer overall public health benefit. But, the Agency, in the absence of support from the sponsor, must refrain from unilaterally switching prescription medicines to OTC status except under the very rare circumstances of overwhelmingly dire public health necessity. The Agency must switch medicines to OTC status by ensuring active participation from all interested parties such as the scientific, medical, pharmacist, industry, public and consumer interest communities in the evaluation of its switch proposals and before reaching a decision to allow OTC marketing. The metaproterenol case proves that the FDA could have enormously benefited in its decision making, if it was aware of the rationale on which opposing groups thought that metaproterenol was not suitable for OTC marketing and objected to its switch. Regardless of the enforcement mechanism (OTC monograph or switch regulation) the Agency must achieve effective participation of all stakeholders in an open and transparent manner before reaching a final decision to allow OTC marketing.

Conclusion

The case of metaproterenol OTC switch by the FDA upon its own initiative offers valuable information in the comprehension of FDA's application of OTC switch regulatory policy. The FDA is encouraged to initiate switch proposals that it considers

to be safe and effective in an OTC environment and offer overall public health benefit. The learning from the failed metaproterenol switch demonstrates that a collaborative effort with the sponsor and all interested parties is more likely to result in a scientifically robust switch decision. Hence, the Agency must properly manage the consideration of switch proposals that it has initiated by ensuring active participation of all possible stakeholders that may be impacted by its rulemaking.

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MANUSCRIPT V

EVALUATION OF PROPOSED OTC SWITCH FOR LOVASTATIN

Abstract

Heart disease is a major cause of mortality among Americans, and the risk factor of cholesterol elevation is well recognized. Making effective drug therapy more readily available to consumers could facilitate improvements in managing this very costly problem. Thus, it has been suggested that making antihyperlipidemic products available over-the-counter (OTC) may contribute a solution. The goal of this article is to describe and evaluate clinical data presented as evidence in determining the benefit to risk ratio of lovastatin in the OTC setting and draw pertinent inferences from this switch case. Based on the lovastatin switch experience, it may be reasoned that for drugs used for chronic illnesses, that require the involvement of a learned intermediary, it may be feasible to favorably balance the benefit to risk by classifying them under an intermediate, pharmacist controlled class of drugs, where a physician's prescription is not required.

Introduction

Heart disease is a major cause of mortality among Americans, and the risk factor of cholesterol elevation is well recognized. Hyperlipidemia affects 50 million Americans and the first approach to lowering cholesterol levels is through lifestyle changes. However, most patients are unable to sustain such lifestyle changes over the long term. Making effective drug therapy more readily available to consumers could facilitate improvements in managing this very costly problem. Thus, it has been suggested that making antihyperlipidemic products available over-the-counter (OTC) may contribute a solution.

Attempts to switch two antihyperlipidemic products from the "statins class" of drugs to OTC status in the United States were made in 2000. One such product was lovastatin (Mevacor®). The goal of this article is to describe and evaluate clinical data presented as evidence in determining the benefit to risk ratio of lovastatin in the OTC setting and draw pertinent inferences from this switch case. The Mevacor® switch case is exceptional and offers key lessons related to application of US Food and Drug Administration's (FDA) OTC switch policy. A detailed review of the Mevacor case history is central to comprehending the current positions of interested parties and FDA's opinion, on switching products to OTC status for chronic illnesses such as hypercholesterolemia.

Background

Lovastatin (Mevacor®) has been marketed in the United States since 1987 as a prescription drug, at doses of 10 mg a day to 80 mg a day. It is indicated for use as an adjunct to diet for the reduction of elevated total and LDL cholesterol (TC and LDL-C)

in patients with primary hypercholesterolemia, when the response to diet restricted in saturated fats and cholesterol and, to other nonpharmacological measures alone has been inadequate. It is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD), as part of a treatment strategy to lower TC and LDL-C to target levels.

The manufacturer of Mevacor presented to the FDA, a switch application describing their rationale for OTC access to lovastatin at 10 mg a day (1). The sponsor's target population consisted of individuals (men over the age of 40 and postmenopausal women) without CHD. The issue of OTCness of cholesterol-lowering drugs was addressed previously at two meetings of joint advisory committees to the FDA in 1995 and 1997, when an application for the OTC switch of Questran[®] (a prescription product that contains cholestyramine resin, which is a bile acid sequestrant antilipemic agent) was discussed and refused. Following the 1997 meeting, FDA published a guidance document indicating that hypercholesterolemia was not an OTC indication (2). The guidance concluded that irrespective of the intrinsic safety and efficacy of the drugs targeting this disease, hypercholesterolemia per se, was not an OTC disease. It also stated that healthcare practitioner supervision was necessary in diagnosis, individualization of treatment, and in follow-up, and that safe and effective use of drugs in this area and the overall treatment of the disease could be assured only within the context of prescription access.

Against this background, the Agency convened a joint meeting of its Nonprescription Drug Advisory Committee (NDAC) and Endocrine and Metabolic Advisory Committee (EMAC) on 13 July 2000 to consider this switch application and

address the "*precedent-setting issues*" raised by the OTC Mevacor petition (3).

Open hearing

Several interested parties strongly endorsed the proposed OTC status for lovastatin during the open hearing (4). Dr. Ernest Madu, Cardiologist and Assistant Professor at Vanderbilt University speaking on behalf of the Association of Black Cardiologists, Dr. Rene Rodriguez, an orthopedic surgeon and President of an organization of Hispanic physicians, Dr. Debra Judelson, an internist, cardiologist and a past president of the American Medical Women's Association, Suzie Hughes, a nurse clinician in the Department of Preventive Cardiology at the Cleveland Clinic Foundation, representing the Board of Directors of the Preventive Cardiovascular Nurses Association, Dr. John A. Gans, Vice President of the American Pharmaceutical Association, Dr. Penny Kris Etherton, a distinguished professor of Nutrition at Penn State University and a member of the second Adult Treatment Panel of the National Cholesterol Education Program (NCEP-ATP II), Brett Kay of the National Consumers League, Dr. Bernie Kasten, Vice President and Chief Medical Officer of Quest Diagnostics Ventures and a pathologist, Mr. Warren Pinckert of Cholestech Corporation, a company that manufactures a point-of-care clinical instrument and has a national testing service, Dr. Tom Pearson, Chair of the Department of Community and Preventative Medicine at the University of Rochester, made statements supporting the proposed OTC switch. In summary, these groups based their endorsement on, the serious need to increase access to medicines to eliminate risk factors for cardiac diseases, the established safety and efficacy profile of lovastatin, surging interest for patient involvement in pharmacotherapy, the availability of technology to rapidly and

easily obtain cholesterol levels by the public, to offer new pharmacological interventions for minorities and medically underserved communities who are at greater risk for cardiac diseases and to make available proven medicines beneficial to the general public who are increasingly using unproven and untested products in the form of dietary supplements and other traditional medicines for cholesterol lowering.

Dr. Sidney Wolfe of Public Citizen's Health Research Group strongly opposed the proposed switch. The basis for this conflicting view was, serious questions about the accuracy of several home diagnostic kits for cholesterol testing because of the inexperience of the user; serious problems in self-selection which would not likely be detected in the real world relative to experimental world where people screen themselves, often without a cholesterol test and decide to use the drug; lack of evidence of cholesterol reduction in any group with a 10-milligram dose and with a 20 to 40-milligram dose the lack of clinical benefit for cases with HDL cholesterol (HDL-C) over 40; diet and exercise may be thought to be less important if the primary strategy is an OTC statin drug; excessive drug interactions associated with lovastatin and an unacceptable benefit-to-risk ratio.

Sponsor presentation

The sponsor stated that OTC lovastatin targets use for primary prevention in a population that was generally not recommended for treatment under NCEP-ATP II guidelines. Specifically, the nonprescription lovastatin treatment population was defined as being men aged 40 and older, and postmenopausal women (at least 1 year past last menses), without CHD and with TC of 200 to 240 mg/dL and LDL-C $\geq$ 130 mg/dL (5). On this basis, the sponsor estimated that there are approximately 15.5 million men and

women potentially eligible to choose self-treatment with nonprescription lovastatin in the United States.

The sponsor justified its request for OTC Mevacor based on: (1) existing guidelines for cholesterol-lowering treatment conserved pharmacological treatment only for those at highest risk for CHD (2) a substantial proportion of CHD events occur in men and women with average TC who were generally not recommended by existing guidelines for prescription cholesterol-lowering treatment, and (3) for motivated men and women in the OTC-eligible population, access to the nonprescription lovastatin treatment program of drug therapy and extensive education and support would provide an effective new option for lowering cholesterol and maintaining cardiovascular health (6).

Efficacy

The benefit of treatment with lovastatin 10 mg daily in the defined OTC population was demonstrated using these approaches (7):

- Observing the effect on lipid parameters associated with CHD risk (i.e., TC, LDL-C, HDL-C and ratio of TC/HDL-C).
- Observing the percentage of OTC eligible men and women who attain desirable levels of TC and LDL-C as defined in NCEP ATP-II guidelines.
- Estimating the effect on reduction of first acute CHD events (defined as fatal or nonfatal myocardial infarction (MI), unstable angina or sudden cardiac death) in the OTC-eligible population.

Results were based on four studies that specifically measured the lipid-modifying efficacy of the lovastatin 10-mg regimen; 2 double-blind, placebo-controlled trials and 2

open-labeled trials. For reference, the efficacy of the 20-mg daily regimen of lovastatin, the usual prescription starting dose, was used. The effects of the 20-mg regimen are based upon data from 2 large, double-blind, placebo-controlled clinical trials: Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and Expanded Clinical Evaluation of Lovastatin (EXCEL).

The sponsor stated that majority of individuals treated with 10-mg daily regimens attained desirable levels of TC (<200 mg/dL). The vast majority treated with 10 mg achieved the NCEP-ATP II goal for primary prevention (68.8% to 75% had LDL-C <130 mg/dL). Notably, 17.4 to 25.7% of individuals treated with 10 mg also attained the goal targeted for secondary prevention (LDL-C <100 mg/dL), and this percentage was similar to the 21.5% observed with lovastatin 20 mg in AFCAPS/TexCAPS. Based on these results, the sponsor asserted that permitting the use of lovastatin 10 mg daily in an OTC population would allow the majority of users to achieve desirable levels of these atherogenic lipids, even without dose titration.

Lovastatin 10 mg/day was the lowest approved prescription dose. Studies in OTC populations revealed that lovastatin favorably modifies lipids by reducing TC-11%, LDL-C-18% and TC/HDL-C-15% and increasing HDL-C-7%. As the OTC-eligible population was defined as having TC <240 mg/dL, LDL-C is expected to be less than 160 mg/dL for a majority of those who are OTC-eligible. With lovastatin 10 mg daily, approximately 70% of OTC eligible men and women could attain levels of LDL-C considered by NCEP-ATP II to be desirable for high risk primary prevention patients (LDL-C <130 mg/dL). The risk of first CHD event was estimated to be reduced by 35% based upon reductions observed in the TC/HDL-C ratio with lovastatin 10 mg daily.

Given these data, the sponsor suggested that lovastatin 10 mg/day represents a conservative but effective and appropriate dose for OTC therapy.

Pharmacology and pharmacokinetics

The sponsor reviewed the human pharmacology and pharmacokinetics of lovastatin to show that, lovastatin is an inactive lactone that, upon hydrolysis, is converted to the β -hydroxyacid (coded L-154819) that is an inhibitor of HMG-CoA reductase (8). Lovastatin and its active metabolite β -hydroxyacid are highly (>95%) bound to human plasma proteins. Lovastatin is extensively metabolized to active and inactive metabolites including, L-154819 and four other lactone: β -hydroxyacid pairs, all of which account for about 80% of the total HMG-CoA reductase inhibitory activity observed in plasma. Lovastatin at the 10-mg dose was not an inhibitor of CYP3A4 ($K_i = 7.7 \mu\text{M}$) in humans. Biliary excretion is an important route of elimination. L-154819 is rapidly cleared from the body (total body clearance and half-life averaged 639 mL/min and 1.5 hours, respectively). The systemic availability of L-154819 following an oral dose of lovastatin is less than 9% of the dose because of first-pass hepatic extraction. The plasma area under the curve (AUC) of active and total HMG-CoA reductase activity increased 2-fold in patients with severe renal impairment (GFR=10 to 30 mL/min). Nonprescription lovastatin was not to be used in patients with renal insufficiency without consultation with a physician. When lovastatin was administered with food, as in clinical studies, the AUCs of active and total inhibitors are about 50% higher compared to administration in the fasting state. For maximum benefit, lovastatin should be given with meals. With lovastatin dosages of 10-, 40-, 60-, 90-, and 120-mg, peak concentrations are achieved in 3 to 5 hours and the AUC and C_{max} of both active

and total HMG-CoA reductase inhibitory activity in plasma increase nearly proportionally with dose. With once-a-day dosage regimens of lovastatin (10,40 or 80mg) there is modest steady-state accumulation of active and total inhibitors in plasma (<10 to 50%). These data indicated that the pharmacokinetics of lovastatin are linear throughout the therapeutic dosage range. Upon co-administration with a potent inhibitor of CYP3A4 (such as itraconazole), the plasma exposure to active or total HMG-CoA reductase inhibitory activity on the 10-mg dose of lovastatin was below the plasma exposure observed following 80-mg of lovastatin, the maximum approved prescription dose. No dose adjustment was required during co-administration of nonprescription lovastatin with less potent inhibitors of CYP3A4, including calcium channel blockers and moderate daily consumption of regular-strength grapefruit juice. Appropriate labeling was proposed to reduce the likelihood that potent CYP3A4 inhibitors will be used concomitantly with nonprescription lovastatin.

Safety

The proposed nonprescription dose of 10 mg has been available by prescription and was estimated to account for approximately 720,000 patient-years of treatment (3% of total use). Long-term, chronic use of lovastatin was generally well tolerated in both EXCEL and AFCAPS/TexCAPS participants (9). The safety profile of lovastatin 20 to 40 mg/day was comparable to that of placebo. A review of the worldwide adverse event data did not reveal a new association between lovastatin and any adverse experience not currently included in the package circular. The spontaneous reports generally reflected the known side effects of the drug (myopathy and aminotransferase elevations), previous warnings within the product circular (lenticular disorders), or concomitant

disease in the patient population (congestive heart failure, myocardial infarction). Dose-proportional increases in hepatic transaminases ($>3 \times$ Upper limit of normal (ULN)) were observed with lovastatin; however, in studies of lovastatin 20 to 80 mg/day, the incidence with 20 mg was no different than that observed with placebo. The spontaneous reporting rate for serious hepatic adverse experiences of heterogeneous pathology was extremely rare, on the order of 10 per million patient-treatment years of lovastatin, did not appear to be dose related, and the relationship to lovastatin is unclear in many of the reports. Routine monitoring of liver function tests (LFT) in users of nonprescription lovastatin was expected to produce a high proportion of abnormal tests which were not indicative of any hepatotoxicity associated with lovastatin. Routine monitoring of LFT did not reduce the extremely low risk of serious liver disease in people taking lovastatin 10 or 20 mg daily. The risk of myopathy or rhabdomyolysis was low and dose related. In clinical trials, the incidence of myopathy in those receiving lovastatin 20 mg daily was similar to that reported for those taking placebo. There were no reported cases of rhabdomyolysis during marketed prescription use of lovastatin 10 mg daily. Myopathy is a rare symptomatic condition that can be recognized by patients with warnings provided in the nonprescription lovastatin label. The condition usually resolved after discontinuation of the drug. There was no apparent association between exposure to lovastatin during pregnancy and the occurrence of any adverse pregnancy outcomes. However, the number of reported cases with a known outcome was small. In view of the limited benefit of this drug in premenopausal women, nonprescription lovastatin was to be indicated only for postmenopausal women and would be contraindicated in pregnancy. The lack of evidence for risk may provide some

reassurance to women who are inadvertently exposed to lovastatin during pregnancy, and to the health care professionals responsible for their care. Other lipid-lowering agents (gemfibrozil and niacin) may increase the risk of myopathy through an unknown mechanism in patients taking any of the HMG-CoA reductase inhibitors. Concomitant treatment with potent CYP3A4 inhibitors may increase plasma HMG-CoA reductase inhibitory activity levels, and therefore may increase an individual's risk of myopathy. The risk of myopathy was very low with lovastatin 10 mg and 20 mg daily regimens, and would be expected to remain low even with concomitant use of a potent CYP3A4 inhibitor. Use of these drugs concomitantly with lovastatin was contraindicated on the nonprescription label.

Long term, chronic use of lovastatin at prescription doses of 10 to 80 mg daily has been well tolerated. In controlled clinical trials, the safety profile of lovastatin 20 mg daily was comparable to that of placebo. Asymptomatic serum transaminase elevations were dose-dependent, and were not proved to progress to clinical liver disease even when drug therapy is continued; the incidence of confirmed ALT elevations ($>3 \times \text{ULN}$) was similar with lovastatin 20 mg daily and placebo. Clinically apparent liver disease (hepatitis, hepatic failure) associated with lovastatin use at any dose was very rare. Therefore, the sponsor argued that routine monitoring of LFT was not of value in users of lovastatin 10 mg once daily. Although myopathy, and rhabdomyolysis are considered the adverse experience of primary concern for the HMG-CoA reductase inhibitors, both clinical study experience and market-use experience indicated that their occurrence is rare. The risk of lovastatin-associated myopathy increased with increasing dose of lovastatin. In postmarketing experience

collaboration with healthcare professionals. The ESP focused before purchase, on the information necessary for consumers to make an appropriate purchase decision and, after purchase on the information needed to refine and extend the understanding of the product and its use. The importance of cholesterol testing and monitoring was emphasized both before and after purchase. Before the purchase decision is made, eligibility criteria for the initial selection of the product was introduced through informative advertising which provides the basic information about who should and should not use the product. The carton label then summarized all information necessary for an appropriate purchase decision. After purchase, the consumer has access to several label reinforcement tools contained within the package that refines the product selection decision. More comprehensive information was available after purchase and educates consumers on the importance of a healthy lifestyle and encourages long-term use in order to maintain the benefit. The core elements of the labels specified the age and stage of life when men and women are at increasing risk of CHD and therefore most likely to obtain the benefit. Also listed were specific values for TC and LDL-C and those who should not use the product reflect the warnings from the prescription labeling.

Additional materials called label reinforcement tools were also provided. These included the package insert, a video-tape which introduces and reinforces the label messages, an information booklet on cholesterol and the importance of maintaining a healthy lifestyle and further communication links beyond the package for the purpose of promoting appropriate use. A key feature of the ESP was the toll-free service which was developed and tested in the sponsor's studies. Use of the toll-free service was encouraged, not only for questions, but for reinforcement of key label messages after

purchase. By talking with the product specialists at the toll-free service, consumers could learn more about their eligibility and appropriate use of the product. This service recommends that consumers with higher risk of heart disease see their doctors and provided an information card to enroll them in the compliance program. The compliance promoting features were a key element of the product which requires long-term use to achieve the benefit. Once enrolled the consumer received a series of regular newsletters with information, aids and the use of Mevacor OTC over the long term in increasing and maintaining a healthy lifestyle. Further, it emphasized the importance of reassessing ones risk profile over the long term. Also provided was a wallet-sized reminder card for tracking lipid changes and avoiding potentially interacting drugs. The product was contained in compliance-promoting calendar packaging. Cholesterol testing and monitoring was encouraged throughout the process and a healthcare professional could help guide the consumer at any time in the process. The first thing consumers recognized upon opening the pack was the need to know their cholesterol numbers. The ESP encouraged consumers to obtain a complete lipid profile and provided guidance on where in the community to have a test conducted. Four increasingly improved versions of the labeling materials were tested in a series of label comprehension tests and in-home use studies. The final label was the one submitted in the NDA. The first three labels were tested sequentially in three in-home use studies conducted in community settings where consumers used the product under simulated real-world conditions. One study was conducted from actual retail pharmacies and allowed long-term use of Mevacor for up to 18 months. Two studies were conducted in rented store space in local shopping centers and tested the toll-free service. Follow-up

surveys were conducted in subsets of study participants in order to supplement the information collected from the clinical studies. A fourth study, was ended early due to poor enrollment. The sponsor also conducted three label comprehension tests finishing with one round of improvements to create the NDA label. These studies showed that effective labeling guided most consumers to make an appropriate selection decision and that the ESP further improves the correctness of that decision to use the product.

The sponsor asserted that consumer behavior testing showed that, (a) most consumers made an appropriate product selection decision (b) accuracy of the product selection decision was further improved when consumers reviewed the label reinforcement tools contained in the package (c) toll-free telephone label reinforcement service was highly effective as a label reinforcement tool (d) results support the conclusion that the nonprescription lovastatin 10 mg labeling system of communication, education and support effectively guides consumer product selection (e) comprehension testing showed that strong scores were achieved on key messages in the general population and the safety subgroup, and that low literacy subgroup scores were also acceptable.

The sponsor stated that even though excellent label comprehension was achieved, additional minor refinements were made to further enhance the final label submitted in the NDA. These minor refinements included: reformatted liver disease and pregnancy warnings for increased prominence; strengthened drug interaction warning text; doctors and pharmacists added as individuals the consumer can contact to determine if they are taking a "Do Not Use" medication; and a caution to consumers with continuing medical conditions that they may need further medical care.

The sponsor concluded that, (a) consumers maintain or improve eating and exercise habits while taking nonprescription lovastatin 10 mg in a nonprescription setting (b) a substantial segment of interested consumers comply well with long-term daily dosing with nonprescription lovastatin 10 mg to achieve clinically meaningful lipid changes, and (c) nonprescription lovastatin labeling system encourages collaboration with health care professionals.

FDA PRESENTATION

QTC population and efficacy

AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled clinical trial designed to demonstrate that treatment with lovastatin 20 to 40 mg every day in 6,605 patients without clinical evidence of CHD and moderately elevated TC and LDL-C and low HDL-C levels would reduce the incidence of a first acute coronary event (composite endpoint consisting of: fatal CHD; nonfatal MI; and unstable angina). After a mean follow-up duration of 5 years, treatment with lovastatin 20 to 40 mg daily in conjunction with a low saturated fat diet resulted in a 37% risk reduction in experiencing an acute coronary event compared to placebo.

The selection of study subjects in the OTC Mevacor development program was based on the sponsor's definition of the target OTC population. A review of the OTC efficacy data by the FDA found that HDL-C level was never specified as a criterion for selecting these individuals from the primary prevention population who would be eligible for treatment with lovastatin (11). AFCAPS specifically enrolled individuals with below average HDL-C levels based on an exclusion criterion specifying that HDL-C levels be <45 mg/dL in males and <47 mg/dL in females. When the estimates of CHD

risk and treatment benefit were summarized in the OTC-eligible subgroup of AFCAPS based on baseline HDL-C levels; of <35, 35 to < 40, and ≥ 40 mg/dL, the risk reductions were greatest in those with HDL-C levels <40 mg/dL. There was no treatment difference seen in those individuals with HDL-C levels ≥ 40 mg/dL who otherwise met the sponsor's definition of being eligible for nonprescription lovastatin treatment.

A subgroup (n=4,092) of the AFCAPS/TexCAPS cohort was selected for baseline lipid levels which matched those of the OTC-eligible population. After excluding for the presence of diabetes and/or use of multiple antihypertensive medications, there were 3,805 patients (57.6%) remaining in the AFCAPS/TexCAPS cohort meeting the eligibility criteria for treatment with nonprescription lovastatin. Of these, 1,884 (49.5%) were treated with lovastatin 20-40 mg daily and 1,921 (50.5%) were treated with placebo. Based on analyses of the AFCAPS OTC-eligible subgroup, treatment with lovastatin 20-40 mg per day for an average of 5 years resulted in a 44% reduction in risk of experiencing an MI, unstable angina, or sudden cardiac death compared to placebo. From these results, the sponsor concluded that treatment with nonprescription lovastatin in the targeted OTC-population could reduce the risk of CHD. FDA asserted that this conclusion may not be valid based on the following:

- The lovastatin dose for which a clinical benefit was demonstrated is 2 to 4 times higher than the proposed nonprescription dose. The LDL-C lowering results associated with the 20 to 40 mg per day dose are not comparable to the nonprescription dose.
- The average duration of treatment in AFCAPS/TexCAPS exceeds the treatment duration observed in any trial conducted in the OTC clinical development program

- The benefit of lovastatin treatment in the AFCAPS/TexCAPS OTC-eligible subgroup was greatest in those with HDL-C levels ≤ 40 mg/dL. In the targeted OTC population, the majority of individuals had HDL-C levels exceeding this value, suggesting that any potential benefit will apply to a much smaller proportion of the target OTC population than estimated by the sponsor.

Based on the data reviewed from studies in the OTC development program and the OTC-eligible AFCAPS cohort, the FDA medical review concluded that the sponsor's proposal cannot be justified for the following reasons (12):

- The clinical benefit of lovastatin treatment observed in AFCAPS was associated with the 20 to 40 mg dose whereas the proposed nonprescription dose is 10 mg. The LDL-C lowering effect of 20 mg in AFCAPS exceeds that of the 10 mg dose observed in the efficacy study.
- The risk reductions associated with lovastatin therapy in AFCAPS was over an average 5-year treatment duration with approximately 70% of those randomized to lovastatin treatment remaining on therapy for this duration. In contrast, the actual-use studies suggest that any potential benefit associated with nonprescription lovastatin use will be limited by the high number of individuals discontinuing treatment after a few months of treatment.
- The potential clinical benefit of nonprescription lovastatin relies on the ability of the consumer to appropriately initiate treatment based on his/her CHD risk profile. The individuals in the primary prevention population most likely to benefit from drug treatment are those with low HDL-C levels. The sponsor did not evaluate whether a

consumer could appropriately initiate drug treatment based on his/her HDL-C level since this criterion was not on the proposed package label.

Hence, the FDA medical review concluded that, *"the aforementioned reasons add significant uncertainty to any estimates of benefit associated with lovastatin 10 mg use in the nonprescription setting. Given the unknown clinical cardiovascular benefits of treating the primary prevention population with the unrestricted availability of lovastatin 10 mg, the benefit-to-risk relationship of this drug in this population cannot be adequately assessed."*

Safety

FDA argued that safety evaluation of OTC lovastatin should not be limited to the 10 mg dose because in the OTC setting due to unrestricted access some individuals will self-titrate. At the 10-milligram dose FDA found that the safety and tolerability of the 10 mg dose of lovastatin to be comparable to that of placebo. And the incidence of myalgias was low and similar across the studies. There were no cases of rhabdomyolysis, myoglobinuria, or liver toxicity reported. At the higher dose of lovastatin, FDA found that consecutive elevations in liver enzymes to more than 3xULN was dose related and at the highest approved dose, the instance was about 1.5 percent, but there were no cases of liver toxicity associated with this enzyme elevation.

FDA contended that the sponsor acknowledged this safety concern, and proposed that this concern can be adequately conveyed to consumers through proper labeling. The sponsors proposal was to warn/advise consumers not to take nonprescription lovastatin if they were on any medications such as erythromycin, clarithromycin, ketoconazole itraconazole, nefazodone, cyclosporin, protease inhibitor,

niacin, gemfibrozil, or any other prescription statin drugs. FDA asserted that this was an extensive list and likely to increase as more drugs are approved. So FDA felt that this method of risk communication was challenging to the consumer. This method of risk communication in the prescription setting was apparently not effective enough to avoid some of the drug-related toxicities. So it raised concern that the proposed method of risk communication for OTC lovastatin may also be ineffective.

A comprehensive review of post marketing safety surveillance of all currently available statins in the United States by the FDA led to the conclusion that a significant concern exists over liver failure associated with HMG-CoA reductase inhibitors given that liver transplants, irreversible and fatal hepatic damage, have occurred. Of the liver failure cases, more than 50% of the patients expired while on lipid-lowering therapy consisting of an HMG-CoA reductase inhibitor. Despite this fatal consequence, the labeling in OTC package inserts did not mention liver failure as an adverse reaction to HMG-CoA reductase inhibitor administration. Additionally epidemiological analysis indicated that the reporting rate of liver failure for the HMG-CoA reductase inhibitors exceeds the background rate for liver failure. Based on the severity of liver failure they recommended that liver failure be included as an adverse event in the labeling of package inserts for OTC lovastatin.

FDA's safety review concluded that, *"Given the fact that there is very little compliance with liver function test monitoring and this class of drugs have been associated with other potentially serious adverse events (including rhabdomyolysis), and have the potential to cause dangerous drug and drug-food (grapefruit) interactions, it is prudent to defer any decision on the OTC switch of these drugs (13)."* FDA opined

that for safety, there are rare, but serious adverse events associated with lovastatin use, particularly that of muscle toxicity which can be potentiated by certain drugs or substances which impair lovastatin's metabolism through the 3A4 isoenzyme. This safety concern was further amplified by the use of lovastatin as a nonprescription drug. As an OTC drug it would be in an unsupervised setting such that the safety of OTC lovastatin is dependent upon the consumer's comprehension of the label, its use according to label instructions, such that there would be no self-titration to higher doses, and no use by individuals at risk for drug-related toxicities.

In evaluating the prescription to OTC switch of lovastatin 10 milligrams, FDA asked the question: What is the balance of benefit versus risk of nonprescription lovastatin? On the benefit side they found LDL-C reduction and agreed that lovastatin does reduce LDL-C. But stated that the effectiveness of this treatment approach in the OTC population will likely be diminished by poor adherence to drug therapy. Another part of the benefit side was that of clinical cardiovascular benefit. FDA asked if drug treatment, in the OTC target population resulted in reductions in cardiovascular mortality and morbidity? And asserted that there is no evidence from controlled clinical trials to demonstrate that. On the risk side, FDA found the safety concerns to be rare, but believed the seriousness of muscle toxicity potentiated by certain drugs and compounded by the unrestricted, unsupervised use of this product in the OTC environment to be excessive and unacceptable.

consumer behavior and labeling

An FDA review of the actual use studies conducted by the sponsor led to these observations (14). The sponsor proposed drug treatment for cholesterol in an OTC

population without CHD. The target population is designed to include healthy subjects who have fewer than 2 risk factors for CHD in addition to subjects who have ≥ 2 risk factors and the protocols use the cholesterol level as a surrogate marker for clinical benefit. The FDA reviewer argued that this population did not meet the NCEP-ATP II guidelines for drug therapy. The AFCAPS/TexCAPS trial, did not demonstrate significant clinical benefit for the < 2 CHD risk factor population who took lovastatin 20 mg or 40 mg. There was no proof that lowering cholesterol with lovastatin 10 mg in the proposed population would decrease the incidence of myocardial infarctions or strokes. In the OTC marketplace, subjects with minimal risk of developing CHD, could choose to take lovastatin 10 mg and thereby place themselves at risk of side effects. The mean HDL in one study was higher than for AFCAPS/TexCAPS. An HDL-C level below 35 mg/dl justifies more intense efforts to lower the LDL-C level. It has been recommended that tailoring therapy to the individual patient be accomplished.

In AFCAPS/TexCAPS, the compliance at approximately 6 months was close to 90%, but there was a steady decline to approximately 71% at the end of the study. It has been demonstrated that a 15% 1-year probability of lovastatin discontinuation was observed for patients in a health maintenance organization setting. In the OTC lovastatin actual use trials, compliance was, 27.6% of subjects discontinued during the first 24 weeks, 31.3% of subjects discontinued the 8 week study and 25.6% of subjects discontinued the 4 week study for three study protocols. This led to the conclusion that subjects who self-prescribe lovastatin 10 mg are not as compliant as subjects who receive their medication from and are followed by a physician.

FDA found that many subjects did not self-select properly with regard to whether they could take lovastatin. This was attributed to not having an accurate knowledge of their cholesterol values or of their concomitant medications. None of the labels were in the FDA required “Drug Facts” format for OTC labeling. The laboratory measurements in the actual use trials were performed on a desktop analyzer, and presumably, this is the way consumers would check their lipid values in a pharmacy when deciding whether to purchase lovastatin. FDA opined that desktop analyzers are fairly accurate on average, but measurements tend to be more variable than those obtained with laboratory methods.

The NCEP-ATP II guidelines recommended a 9-12 hour fast as opposed to a 2-hour fast. Because of variability in measurements, as per NCEP-ATP II guidelines, and as was done in AFCAPS/TexCAPS, subjects should have had at least, two blood samples analyzed for lipids to determine drug eligibility. As OTC consumers would not comply with enough, properly fasted, cholesterol measurements to provide an accurate determination of their baseline cholesterol profiles, this would argue against the appropriateness of OTC self-diagnosis and treatment.

The FDA review found the design and results of the actual use trials to be inadequate in the following ways:

1. Since the HDL value is an important determinant of risk for CHD, it should be included as a factor to determine who can take lovastatin 10 mg. Consumers should be tested to determine if they understand the meaning of their HDL level and can appropriately use this information as a factor in self-selection.

2. A single cholesterol test performed without a proper fast is a poor way to decide whether someone should take lovastatin 10 mg. The sponsor should demonstrate that proper screening methods and compliance can be achieved in the OTC setting.
3. The labels did not provide sufficient information to use the product effectively. Self-selection errors were too frequent. The safety information was incomplete because laboratory data (especially LFT and creatinine phosphokinase (CPK)) was not provided.
4. The compliance rate in the OTC setting was poor. This would probably impact on any long-term benefit to be derived from taking lovastatin 10 mg in this population.
5. A long-term clinical benefit of taking lovastatin 10 mg in the population at low risk for CHD (especially those with < 2 risk factors) has not been demonstrated.

FDA review of the label comprehension studies observed that the studies covered the communication objectives with questions that, in most cases, do not require participants to do more than repeat or identify the presence of information on the label. Hence, FDA opined that it is not possible to determine how well consumers can use the information and interpret it correctly. In particular, there were no questions to determine if participants understood that they must meet all three criteria to use the product: TC of 200-240, LDL-C ≥ 130 , males > 40 years and females at least 1 year past menopause. The reviewer stated that it was likely that questions requiring participants to apply the information on the label to hypothetical situations would have produced lower scores, but would have given a better assessment of how well the label is understood. The results indicate that there may not be good understanding of who cannot take the product, including men under 40 and pre-menopausal women.

As the phrasing of the question on this issue permitted responses that the information was not on the label it was difficult to know if participants understood well who could not use the product if the information was not on the label. Results about who should not use the product, coupled with the incomplete information on participants' understanding about who can take the product, raised concerns about appropriate self-selection. FDA found although a few scores improved substantially after participants read the materials inside the package, correct responses remained in the 74-77% range for questions about pre-menopausal women and men under 40, and improved scores after reading all the materials may have been due to the study methodology rather than the effect of the additional materials.

Further, the questionnaire collected information about the personal health status of participants, participants were never asked if they could use the product themselves. This information would have been useful in determining how well consumers could self-select and might have overcome some of the shortcomings of the other questions about who could and could not use the product. The low literate participants had problems understanding some of the important messages. They had particular problems understanding if Mevacor OTC can be used by persons with various total TC and LDL-C levels and by women before menopause. The reviewer concluded that this study does not provide sufficient information to state confidently that consumers can self-select to use the product appropriately; or, whether they understand key information such as they must check cholesterol after beginning use.

COMMITTEE DISCUSSION

Based on the presentations made by the sponsor and the Agency, FDA posed a

list of questions to the committees that have been presented in table 1 (15). The committees deliberated each question and voted a yes or no response to each question. The first question related to the "clinical benefit" of lovastatin 10 mg was split by the committee into two parts for clarity. When clinical benefit was defined, merely, as the lowering of LDL-C, the committee unanimously voted in agreement (13-yes; 0-no; 0-abstained). But, when clinical benefit was defined as reducing cardiovascular events, the committee voted strongly in dissent (1-yes; 12-no; 0-abstained). This split vote showed that the committee did not endorse the sponsor's rationale of using lowering of LDL-C as a surrogate marker for reduction in cardiac events to demonstrate the clinical benefit of OTC lovastatin. Further, the committee stated that a placebo-controlled clinical trial in the target population with cardiovascular endpoints should be conducted to demonstrate clinical benefit.

The second question was on the global safety, not merely the OTC population, of 10 mg dose of lovastatin. On this question, the committee was unanimous in endorsing the safety of 10 mg lovastatin (13-yes; 0-no; 0-abstained). Question three was on the balance of benefit and risk of OTC lovastatin, and due its close similarity to the earlier two questions, the committee decided not to vote on this question. On question four the committee unanimously voted (0-yes; 13-no; 0-abstained) that the sponsor failed to demonstrate that consumers could achieve a clinical benefit in an OTC setting. The major reasons for this dissent were inability to self-select and understand the need for lifelong therapy by the consumers. Question five was on the demonstration of safety of lovastatin in the OTC setting and seven members thought it was safe, whereas six others thought it was not safe (7-yes; 6-no; 0-abstained). Some reasons for the

dissenting vote were possible self-titration leading to overdose, lack of evidence showing effective communication to ineligible population, potentially numerous interacting drugs and the inability of consumers to see a physician when required.

The committee modified question 6 to, has the sponsor provided sufficient evidence that lovastatin 10 milligrams can be used safely and effectively in an OTC setting? This question was answered in strong dissent by the committee (1-yes; 11-no; 1-abstained). In terms of additional studies to demonstrate approvability of OTC lovastatin, the committee made these suggestions:

- Demonstrate efficacy using better defined eligibility criterion and using LDL-C as a surrogate marker relative to prescription lovastatin use.
- Study actual use in a wholly unrestricted manner to demonstrate ability of consumers (to cover minorities, ethnic and low literacy populations) to self-select, self-deselect safely and effectively the proposed OTC medicine.
- Survey large groups to determine their interest in lipid-lowering agents, the obstacles involved with using such drugs and if inadequate medical care is considered an obstacle.
- Study the ability of consumers to self-titrate to larger doses in a safe and effective manner.

Conclusion

Elevated cholesterol is an important risk factor for cardiac disease in the United

States. The public health significance of cholesterol-lowering drugs is intensifying and NCEP recently issued major new clinical practice guidelines on the prevention and management of high cholesterol in adults (16). One of the key changes in the new guidelines is the emphasis on aggressive cholesterol-lowering treatment. Despite the renewed accent on pharmacological intervention in cholesterol management, growing public support for OTC antihyperlipidemics, and, free and widespread availability of some cholesterol lowering agents in the form of virtually unregulated dietary supplement products, the Agency's current position is that hypercholesterolemia is intrinsically a non-OTC indication. Along with the lovastatin switch petition, FDA advisory committees also refused to approve a similar OTC switch petition for pravastatin (another prescription cholesterol lowering drug from the statins class). FDA maintains that safe and effective use of drugs in this area and the overall treatment of the disease could be assured only within the prescription setting where access to a learned intermediary is readily available.

It is possible to reason that for drugs such as these, used for chronic illnesses, where FDA maintains that the involvement of a learned intermediary is necessary, it may be feasible to favorably balance the benefit to risk by classifying them under an intermediate, pharmacist controlled class of drugs, where a physician's prescription is not required, but pharmacists may dispense medication based upon patient consultation and their professional judgment. Such an intermediate class of drugs presently does not exist as per the current United States classification system, but other developed nations such as Canada, United Kingdom and Australia allow for this class of nonprescription medicines. However, the creation of such a pharmacist class of nonprescription

medicines in the United States would require legislative action to amend the Food, Drug & Cosmetic Act. Also, as more potent molecules become candidates for reclassification to OTC status, the intermediate class of drugs may facilitate the achievement of an acceptable benefit to risk ratio in the nonprescription setting.

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Table 1: List of questions posed by FDA to its advisory committees on the proposed OTC status for lovastatin 10 mg

<i>Efficacy and Safety in the Proposed Target Population</i>
<p>1. The sponsor proposes an indication, based upon an expectation of cardiovascular benefit, for the use of lovastatin 10 mg in individuals with TC 200-240 mg/dL and LDL-C > 130 mg/dL, regardless of HDL-C level, and without CHD or diabetes. Current guidelines for the treatment of hypercholesterolemia do not target such individuals for drug treatment. Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit of lovastatin 10 mg in the target population?</p> <p>a. If yes, what is the nature and magnitude of the benefit?</p> <p>b. If no, what additional data are needed to demonstrate a clinical benefit in the target population?</p> <p>2. Statins have been associated with myopathy, including rare cases of rhabdomyolysis, as well as with elevations in hepatic transaminases (although the association between use of these drugs and serious hepatic disease is less clear). Intercurrent illness, undefined individual susceptibility factors, and interactions with other drugs and/or foods may increase the risk for rhabdomyolysis with statins. Taking into account these and other safety issues, has the sponsor presented adequate data to support the safety of lovastatin 10 mg in the target population?</p> <p>a. If no, what additional data are needed to demonstrate safety?</p> <p>3. Taking into consideration the balance of risk and benefit, has the sponsor presented data that are adequate to support the use of lovastatin 10 mg in the low-risk population with TC 200-240 mg/dL, LDL-C > 130 mg/dL, regardless of HDL-C level, without CHD or diabetes?</p> <p>a. If no, what additional data are needed to support such an indication?</p>
<i>OTC Considerations</i>
<p>4. Assuming an indication for the use of lovastatin 10 mg in the proposed target population can be justified based upon an expectation of clinical benefit, has the sponsor adequately demonstrated that consumers can achieve such a clinical benefit in an OTC setting? In responding to this question, please consider the following:</p> <p>a. The ability of consumers to appropriately self-select (and de-select) based upon cholesterol levels and other risk factors.</p> <p>b. The ability of consumers to evaluate response to treatment and to monitor cholesterol levels (including understanding of how to undertake a fast and the frequency of re-testing).</p> <p>c. The ability of consumers to adhere to chronic therapy with lovastatin 10 mg.</p> <p>d. The need for the physician or other healthcare professional in the effective treatment and follow up of dyslipidemia.</p> <p>e. The capacity of the proposed label to direct consumers in the effective use of lovastatin 10 mg OTC.</p> <p>5. Assuming that lovastatin 10 mg is deemed adequately safe when used for the proposed indication in the target population, has the sponsor presented adequate evidence that consumers will be able to use lovastatin 10 mg safely in an OTC setting? In responding to this question, please consider the following:</p> <p>a. The ability of the consumer to identify adverse reactions to lovastatin and to act appropriately.</p> <p>b. The ability of the consumer to monitor hepatic safety including the need for monitoring of hepatic transaminases and the ability of the consumer to perform such monitoring if needed.</p> <p>c. The need for and ability of the consumer to identify and avoid interacting drugs and other substances.</p> <p>d. The likelihood of use of lovastatin 10 mg at higher than recommended doses (1 tablet per day).</p> <p>e. The ability of women who are pregnant or likely to become so to appropriately avoid use of lovastatin 10 mg.</p> <p>f. The need for the physician or other healthcare professional in the safe treatment and follow up of dyslipidemia.</p> <p>g. The capacity of the proposed label to direct consumers in the safe use of lovastatin 10 mg OTC.</p>
<i>Approvability</i>
<p>6. Assuming that the answer to Question 3 is yes (i.e., the sponsor has provided sufficient information to support the safety and effectiveness of lovastatin 10 mg for the proposed indication in the target population), has the sponsor provided sufficient evidence that lovastatin 10 mg can be used safely and effectively in an OTC setting?</p> <p>a. If yes, are any additional studies needed post-approval? What are the key messages that need to be conveyed to the consumer in the product label (carton and package insert) to provide for the safe and effective use of lovastatin 10 mg OTC?</p> <p>b. If no, what additional studies are necessary to support approval for OTC marketing?</p>

MANUSCRIPT VI

EXAMINATION OF PROPOSED OTC STATUS FOR NONSEDATING ANTIHISTAMINES

Abstract

Loratadine, fexofenadine and cetirizine are orally active H₁-receptor antagonists that do not have the sedating side effects of earlier antihistamines like chlorpheniramine. In 1998, Wellpoint Health Networks filed a citizen petition with the FDA to request the reclassification of certain marketed products containing these second generation antihistamines to over-the-counter status in the United States. Contrary to common practice, this switch request did not originate from the manufacturers of these drugs. This remarkable departure from conventional practice related to the switch process makes this citizen switch petition unprecedented in nature. The unparalleled nature of this case raises many significant regulatory, safety and legal issues related to OTC switch process in the United States. This article aims to present an objective and detailed examination of the regulatory and safety issues related to this OTC switch petition.

Introduction

Loratadine (LR), fexofenadine (FX) and cetirizine (CZ) are orally active H₁-receptor antagonists that do not have the sedating side effects of earlier antihistamines like chlorpheniramine (1). They are commonly referred to as "*second generation antihistamines*" and are currently available, only by prescription, in the United States. LR is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and treatment of chronic idiopathic urticaria (CIU). FX is indicated for the relief of symptoms associated with SAR and treatment of CIU. CZ is indicated for symptomatic relief from seasonal and perennial allergic rhinitis (SAR and PAR), in addition to CIU treatment.

In 1998, Wellpoint Health Networks filed a citizen petition with the FDA to request the reclassification of certain marketed products containing LR, FX and CZ to over-the-counter (OTC) status in the United States (2). This article aims to present an objective and detailed examination of the regulatory and safety issues related to this OTC switch petition.

Background

To elucidate the unprecedented nature of this OTC switch petition, it is beneficial to describe the underlying rationale for the prescription requirement and the general OTC switch process in the United States. The principles based on which medicines are classified into, OTC or prescription status, in the United States originate from the Durham-Humphrey amendment to the Food, Drug and Cosmetic Act (FDCA) in 1951. This amendment clarified the dispensing obligations of the pharmacist by defining the kinds of drugs that cannot be safely used without medical supervision and

restricting their sale to prescription by a licensed practitioner (3). An implication of section 503(b)(1) of FDCA, which needs emphasis, is that drug products are inherently presumed to be nonprescription unless otherwise required. This assertion is generally stated as, "*if it can be OTC, it must be OTC*" to illustrate the inherent bias for "nonprescriptionness" arising from the law and is critical in the context of the current discussion (4).

Traditionally, prescription drugs have been reclassified to OTC status via, either the OTC monograph process or an OTC switch petition in the form of an NDA. When FDA initiated the OTC Drug Review in 1972, the monograph process resulted in many drugs being reclassified to OTC status. More recently, drugs have been switched to OTC status upon approval of manufacturer initiated switch petitions (NDA). However, the current request to reclassify certain products of LR, FX and CZ to OTC status did not originate from the manufacturers of these drugs. An independent party, other than the drug manufacturers, requested the FDA to approve the proposed OTC status for these nonsedating antihistamines. This remarkable deviation from conventional practice related to the switch process makes this citizen petition for OTC status of LR, FX and CZ unprecedented in nature. The unparalleled nature of this case raises many significant regulatory, safety and legal issues related to OTC switch process in the United States.

Rationale and basis of citizen petition

The regulatory basis for this citizen petition to request OTC status was 21CFR§10.30 and 21CFR§310.200, wherein, any interested person may petition the FDA for regulatory action, and, drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA-Commissioner determines the prescription

requirements to be unnecessary for the protection of public health. Additionally, the petitioner provided the following medical and pharmacoeconomic rationale to justify the request (2):

- Of the 3.5 billion health problems treated annually, almost 2 billion (or 57%) are treated with OTC drugs as primary or major adjunctive therapy. The current restrictions limiting OTC access to antihistamine and antihistamine/decongestant medications with a higher incidence of sedation and anticholinergic side effects is dangerous and costly.
- Americans are 4 times as likely to purchase an OTC medication as they are to consulting a physician. Many patients cannot afford the office visit associated with a physician. The current restrictions precluding OTC access to antihistamine and antihistamine/decongestant medications with a lower incidence of side effects predisposes many patients to dangerous antihistamine and antihistamine/decongestant treatment options.
- Almost 60% of all dosage units consumed by patients are for OTC medications. Over 500 medical conditions are treatable with one or more OTC medications as the primary therapy or major adjunctive therapy. These conditions occur millions of times each year (e.g. cold, allergy, and nasal congestion). The current restrictions precluding OTC access limits many patients to dangerous antihistamine and antihistamine/decongestant treatment options.
- Requiring that a patient schedule an office visit to obtain safe medications is an undue time and financial burden to the patient. Additionally, requiring a prescription

for these safe antihistamine and antihistamine/decongestant combinations trivializes the patient-physician relationship.

- Based on recent historical precedent, the cost of the OTC versions of the drugs listed above will be 50% of the prescription drug cost.

Advisory committee meeting

To decide upon this citizen petition and seek advice on the suitability of LR, FX and CZ for OTC status, the FDA convened an open meeting of its Nonprescription and Pulmonary-Allergy Drugs Advisory Committees on 11 May, 2001 (5). FDA informed the advisory committees that the intent of this meeting was to seek advice on whether LR, FX and CZ, given their marketing history, safety profiles, and that they are in a class of drugs already accepted for OTC availability, could be used appropriately and safely by consumers without the intervention of a learned intermediary. FDA clarified that it is not, seeking advice on the economic considerations of this switch (as this is not within the purview of the FDA), or, seeking debate on the regulatory and statutory basis for a FDA-initiated switch to OTC status, from its advisory committees. Hence, the FDA presented questions only on the safety of LR, FX and CZ in the OTC setting to its advisory committees for voting. These questions are tabulated in table 1.

Sponsor's position

The manufacturers of LR and FX participated in the public hearing, whereas the manufacture of CZ declined the invitation to join the meeting. The manufacturer of LR asserted that OTC status is inappropriate for these drugs and submitted the following as major reasons to justify their position (6):

- The citizen petition did not provide data of the type or rigor that is required to support an OTC switch. The petition relied solely on anecdotal safety evidence from a Canadian adverse drug reaction database and a meta-analysis that inappropriately combined data from clinical trials with differing methodologies. Further, data pertinent to actual OTC use would have to be generated and additional analyses conducted for proper assessment of safe and effective use without a physician's supervision. This would include prospective studies to investigate the expected therapeutic index for drug use in an OTC setting, as well as estimates and evaluation of the probability of various adverse outcomes.
- The complexity of proper diagnosis and treatment of allergic diseases, as well as associated comorbid conditions, suggests that self-care may often be inappropriate and that labeling to ensure safe and effective OTC use cannot be developed without further study. Prescription status may well be necessary to protect and optimize public health. As compared to when earlier antihistamines were made available OTC, there is a dramatically different understanding today of the seriousness of allergies, their pervasive effects on health and quality of life, and most notably, their very high association with other serious comorbidities. In particular, a strong relationship with asthma has now been documented, as well as an association with sinusitis and otitis. A thorough medical evaluation with identification of environmental allergens and clinical or subclinical comorbid conditions is essential for optimal treatment outcomes.
- The safety profile of second-generation antihistamines in an OTC setting is not fully known. Although safety is well established for prescription use, significant issues

require further study to ensure that equivalent safety would exist without a physician's care. The absence of a physician or pharmacist as an intermediary who would be aware of a patient's concomitant medications is a concern. The pharmacokinetic interaction and safety profile for each of the second-generation antihistamines is different and each of the antihistamines must be considered and evaluated independently. Other aspects of the pharmacologic profile of these drugs also warrant more specific evaluation, particularly were the drugs to be used without physician oversight. The history of this class of drugs is one in which unexpected interactions have been discovered many years after use by millions of patients.

The manufacturer of FX, in contrast to LR's sponsor, did not argue that OTC status was completely inappropriate for FX. Instead, they took the position that it was premature to make an objective assessment of its OTC suitability, as FX was approved only in July-1996 for U.S. marketing. To justify their cautious approach, they cited the example of an earlier non-sedating antihistamine terfenadine (TF is the parent drug that is metabolized to FX). TF was initially approved in the U.S. as a prescription drug and was later considered for OTC status. However, within the first several years of marketing, a serious safety concern related to cardiac arrhythmias eventually resulted in TF being withdrawn from the U.S. market.

Medical community's position

The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology were strongly opposed to the non-sedating antihistamines being moved to OTC status. The rationale for their position was as follows (7):

- Contrary to the purpose of this switch petition, if approved, the placement of these compounds on the OTC market will result in a reduced availability of these valuable medications to patients. The cost of these drugs will likely make them unavailable to those patients who received them through insurance covered formularies.
- OTC availability will eliminate the physician from the care process of patients taking antihistamines. The appropriate use of these medications needs the reinforcement of health care providers with expertise about allergic disorders. Overuse or misuse of this class of drugs for disorders in which they have no proven efficacy will increase health care costs. Conversely, underuse in appropriate allergic disorders will negatively impact their effectiveness and result in poorer outcomes. Furthermore, the drugs being considered are not necessarily equivalent in their efficacy or their capacity to induce sedation, or cognitive and performance impairments depending on the dose.
- Allergies are not necessarily a self-diagnosable condition. Although 20-30% of the U.S. population suffers from allergic disorders, public surveys indicate that up to 75% of people feel they have allergies. This leads to the overuse of antihistamines for disorders where they have no proven efficacy. By placing these agents in an OTC status this problem will be compounded.
- Subjects with allergic diseases often fail to adequately appreciate the degree of impairment they have from their disease as well as whether treatment impacts upon this impairment. By placing these agents in an OTC status, physicians will not play as active a role as they should in assessing disease status and response to therapy. By placing these agents in an OTC status, in some cases there may be a resultant

trivialization of the disorders for which they should be utilized. Reduced availability or utilization of these drugs without physician evaluation may mask or delay appropriate diagnosis of underlying disorders such as sinusitis, otitis, or asthma. As well, urticaria can be a manifestation of a serious underlying condition, which if left undiagnosed, could lead to substantial morbidity and mortality.

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) stated that a physician and pharmacist is necessary in the responsible use of non-sedating antihistamines and did not support the proposed OTC status (8). Further, they opined that allergic rhinitis (AR) may not be self-diagnosed as nasal polyps or tumors could be the problem.

FDA's position

The Agency asserted that AR and related conditions are generally considered amenable to self-diagnosis and self-treatment (9). Antihistamines as a class have a long history of OTC availability and are used in these indications, with correct usage guided by OTC monograph labeling. Hence, FDA reasoned that neither an actual use study nor a label comprehension study was required to support the proposed OTC switch petition for LR, FX and CZ. Further, FDA opined that it is not appropriate that these drugs be switched to OTC status for all age ranges, formulations and/or indications for which they are approved for prescription use. For instance, CIU, an approved prescription indication for all three drugs was not considered to be an appropriate OTC indication. Also, FDA stated that the efficacy of this class of drug products and the appropriateness of antihistamines in general for OTC marketing is not in question. The Agency took the

position that efficacy of these drugs is not in question as there is a long history of OTC marketing of antihistamines.

Hence, FDA's OTC switch review team conducted an extensive review of worldwide safety information related to LR, FX and CZ to determine whether there are safety concerns that might preclude their appropriate use in the OTC marketplace. The safety data for all three drugs were derived from the NDA safety databases, the spontaneous reporting system (AERS) database, and the published literature (10). FDA concluded that a thorough review of all available data, from its own safety information and from countries where LR was available without a prescription, failed to identify conclusive evidence of a causal relationship between use of LR and serious adverse events. It must be clarified that countries where LR is available without a prescription allow for a third class of drugs, which require dispensing, only in a pharmacy under the supervision of a registered pharmacist. Under the current US classification system, there does not exist a comparable class of medicines. Hence, it must be emphasized that even in countries where LR is available without a prescription, the involvement of a learned intermediary is not completely eliminated. Potential safety signals were noted for ventricular arrhythmias and liver failure; however, the data were deemed as inconclusive and suggested that if such events were causally related to LR, they are extremely unusual. A potential association between LR use and seizures was observed, consistent with information contained in the current package insert, and likely consistent with a class effect.

FX is the active metabolite of TF, but lacks the pro-drug's ability to inhibit the main subunit of the potassium channel *in vitro*, which is felt to be the primary

mechanism responsible for cardiac arrhythmias associated with TF use. As the sole active metabolite, FX is predicted to have a non-cardiac adverse events profile reflective of TF, and to be safe from a cardiac perspective. A full safety review of TF, excluding cardiac events, was also conducted by the Agency to supplement the available post-marketing data available for FX. For FX, the Agency concluded that a detailed review of all available safety data did not reveal evidence of a causal association between FX use and serious and/or life threatening adverse events. A possible association between FX use and seizures was noted that is not currently reflected in the package insert. A potential signal of ventricular arrhythmias in association with FX use was detected, however, the data was thought to be inconclusive and the known pharmacologic properties of FX argue against a causal link.

CZ is an active metabolite of hydroxyzine, a currently marketed prescription antihistamine. Upon an extensive review of adverse event reports associated with use of CZ, FDA found possible associations between CZ and sedation, neuropsychiatric events, including seizures, cardiac arrhythmias, and thrombocytopenia. The Agency thought that there is a preponderance of neuropsychiatric adverse events, particularly sedation, which may exceed the rate of reporting of similar events for LR and FX. The Agency reviewers felt that the data were inconclusive with regard to a causal relationship between CZ and arrhythmias and thrombocytopenia.

FDA also reviewed the post-marketing surveillance data related to first generation antihistamines and compared the observations with those of the drugs in question. Overall, the Agency made the inference that although generally accepted as appropriate OTC drugs, the first generation antihistamines agents possess a number of

safety concerns, some of which are serious, in addition to their widely recognized sedative and cognition-impairing properties. Although the occurrence rates of adverse events attributable to the OTC antihistamines cannot be directly compared to those of LR, FX or CZ due to many potential confounders, the Agency suggested that these three products might offer certain safety advantages over the currently available first generation antihistamines, primarily with regard to sedation and cognition.

Advisory committees' recommendation

Based on the above-described positions, testimony from other interested parties and their own deliberation; the advisory committees voted 19-4 endorsing acceptable safety profile in an OTC setting for LR and CZ. For FX, the panel voted 18-5 in favor of an acceptable OTC safety profile. Members of the advisory panel that voted in dissent reasoned that the lack of data from actual-use studies does not allow an accurate assessment of the benefit-to-risk ratio for these drugs in an OTC setting. The committees deliberated upon the nature of labeling that may be required to facilitate effective consumer communication. The consensus agreement was to use the existing labeling from the final antihistamine monograph, with some modifications. The committees suggested that a warning statement on sedation be included for CZ. Additionally, several committee members also recommended contraindications for consumers with renal and hepatic disorders; in particular, elder patients were suggested to see the physician before use.

Discussion

As stated earlier in the article, this unprecedented switch petition and FDA's consequent action lead to significant questions pertaining to the OTC switch process in

the United States. Two such questions relevant in the present context are, (a) *Under what circumstances should FDA actively propose OTC marketing for a drug in the absence of support from a sponsor?* and (b) *Should FDA be more active in initiating switches of prescription products to OTC use?* In fact, as part of an ongoing review of the Agency's approach to regulating OTC drug products that began in June 2000, FDA has solicited public comment on these two questions (11). In responding to these questions, it is necessary to ascertain if FDA has the statutory right to propose OTC marketing of a drug product. This author opines that FDA has the statutory authority to propose OTC marketing of a drug product. The basis for this opinion is 21CFR§310.200(b) also known as the "switch regulation" and section 503(b)(3) of FDCA. As per 21CFR§310.200(b),

"Any drug limited to prescription use under section 503(b)(1)(c) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling."

Section 503(b)(3) of FDCA states,

"The Secretary may by regulation remove drugs subject to sections 502(d) and 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health."

As stated earlier, Section 503(b)(1) of FDCA states the prescription-dispensing requirements and Section 505 of FDCA describes the pre-marketing approval

requirements and process for drugs. Additional evidence in favor of this opinion is found in the Agency's response to metaproterenol controversy (12). In 1983, as part of the OTC Drug Review the Agency allowed OTC marketing of metaproterenol sulfate, but later, due to the advisory panel's recommendation against the OTC status for metaproterenol, rescinded upon its earlier decision to allow OTC status for metaproterenol. In explaining that action, FDA wrote that although it agreed with the advisory committee's recommendation on that occasion, it did not believe that all drug decisions require the prior involvement of an advisory panel or notice-and-comment procedures. The Agency asserted that Congress has given the duty of approving drugs to FDA and argued that it has the statutory responsibility to make a broad range of decisions (related to safety, efficacy, prescription or OTC status, indications for use and labeling of drugs) involving the suitability of drugs for use by the American public.

Also, according to FDCA all medicines are inherently assumed to be nonprescription in nature and the prescription restriction is applied only when necessary to safeguard public health. Extending this rationale to the current situation, wherein both the Agency and its advisory committees have endorsed the safety of these drugs in an OTC setting, it is possible to reason that FDA may remove the prescription requirement for LR, FX and CZ. One implication of applying the "*if it can be OTC, it must be OTC*" rationale to this situation is as follows and deserves explanation. It is well known that descarboethoxyloratidine (DCLR) is a major active metabolite of LR. If an interested party requests marketing approval for DCLR in a separate NDA to the Agency under prescription category, FDA will then be compelled to grant OTC status for DCLR also. As DCLR and LR have the same pharmacological safety and toxicity

profiles, it would be inconsistent if FDA granted OTC status for LR and approved a prescription NDA for marketing DCLR, LR's active metabolite. Based on this reasoning, it may be inferred that FDA has the authority to reclassify drugs to OTC status. But, it remains unclear as to what regulatory mechanism the Agency may employ, should it decide to allow OTC status for these drugs.

In relation to nonsedating antihistamines FDA has taken the position that neither an actual-use study nor a label comprehension study is required as AR is a known self-diagnosable condition and an OTC antihistamine monograph exists. In the absence of data from an actual-use trial it remains unclear how the target OTC population for these medicines can be determined. Also, the duration of use after which consultation with a physician is required is unknown for these drugs. The use of second-generation antihistamines tends to be chronic in nature and a warning of short duration of use may be inappropriate (9). In this regard, FDA's position presents a dramatic departure from its rigorous data and evidence based decision-making approach that was employed in evaluating recent switch petitions.

The position of this author is that FDA should initiate switch proposals that it considers to be safe and effective in an OTC environment and offer overall public health benefit. Also, the Agency must switch medicines to OTC status by ensuring active participation of all interested parties such as scientific, medical, pharmacist, industry, public and consumer communities in the evaluation of its switch proposals and before reaching a decision to allow OTC marketing. The author believes that the drastic regulatory action of FDA switching a product to OTC status despite the sponsor's objection should be carried out only under very limited and highly unusual

circumstances. Such a situation may be an enormous and overwhelming support among the general public and other stakeholders for OTC availability of a certain product, assuming it meets all the safety, effectiveness and labeling standards required of any OTC products.

Conclusion

The citizen petition for OTC status of these nonsedating antihistamines demonstrates a remarkable deviation from common practice related to the switch process in the United States and makes this citizen petition unprecedented in nature. The unparalleled nature of this case raises many significant regulatory, safety and legal issues related to OTC switch process in the United States.

Based on overall review of the safety profile of LR, FX and CZ, the Agency concluded that these drug products, in the OTC setting, might offer certain safety advantages over the currently available first generation antihistamines, primarily with regard to sedation and cognition. FDA also took the position that no actual use trials or label comprehension trials are needed to support this switch request as they fall under an existing OTC monograph for antihistamine products. The Nonprescription and Pulmonary-Allergy Drugs Advisory Committees to the FDA voted strongly in favor of these drugs meeting the safety profiles required for unsupervised use in an OTC environment.

It may be inferred that FDA has the authority to reclassify drugs to OTC status. However, it remains unclear as to what regulatory mechanism the Agency may employ, should it decide to allow OTC status for these drugs. This author believes that the drastic regulatory action of FDA switching a product to OTC status despite the

sponsor's objection should be carried out only under very limited and highly unusual circumstances.

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MANUSCRIPT VII

ATTITUDES AND OPINIONS TOWARDS REGULATORY ASPECTS OF NONPRESCRIPTION MEDICINES: PART 1

Abstract

The objective of this study was to examine the attitudes of stakeholders on issues related to regulation of nonprescription medicines. The study was designed as an internet based electronic survey questionnaire. The attitudes of 473 participants in the United States, Australia, the United Kingdom and Canada were measured using their stated responses on issues related to regulatory aspects of nonprescription medicines using a five-point Likert scale. A majority (65%) of responses came from the United States whereas other responses were roughly equally distributed between Australia (10%), United Kingdom (12%) and Canada (13%). Response rates of 17% and 7% were observed for the two respondent cohorts from the United States and outside United States respectively. Responses from all four countries show ambivalence towards the role of regulatory agencies in initiating switches or unilaterally switching medicines to nonprescription status without the sponsor's support. Respondents unanimously stated that risks and benefits to individuals and public health must be the paramount criterion in rendering decisions on availability of new OTC medicines. A substantial majority of all respondents believed that chronic illnesses (such as asthma), diseases that require initial diagnosis by a physician (such as hypercholesterolemia) and diseases such as hypertension are unsuitable for self-treatment. Respondents also firmly believed that diuretics, antihypertensive drugs, oral antidiabetic drugs, antimicrobials, cholesterol-lowering drugs, osteoporosis medications and oral contraceptives are not appropriate for self-medication. Respondents believed that the consumers do not possess the knowledge or ability to ensure responsible use of potent nonprescription medicines without the help of a learned intermediary.

Introduction

The growing global interest in self-medication and the potential economic benefits accentuate the necessity for a regulatory framework developed on the basis of sound scientific principles. Hence, this area is beginning to receive much attention from global regulatory authorities. The US Food and Drug Administration (FDA) is currently examining its overall approach to regulating over-the-counter (OTC) drug products and has conducted a public hearing to solicit information from interested persons including scientists, professional groups, and consumers (1). The FDA listed specific questions related to regulatory aspects of OTC drug products upon which it requested comments of all interested groups (such as pharmacists, academicians, physicians, consumers and pharmaceutical industry).

The primary objective of this investigation is to develop answers to questions that FDA has posed (on issues such as the OTC regulatory environment, role of regulatory agency in Rx-to-OTC switches, criteria for OTC classification, suitability of drugs for OTC status and disease conditions for self-medication, consumer behavior and understanding of OTC medicines and the approval of new OTC medicines) using the responses of some stakeholders in the United States, Canada, the United Kingdom and Australia. A second aim was to use the data collected to gain insight into the opinions of a subsection of stakeholders interested in the regulation of OTC drug products.

Methodology

Study participants: Requests for participation in the study and the web address of the questionnaire were forwarded by email to all listed faculty members in pharmacy practice and pharmacy administration departments in the United States, United

Kingdom, Canada and Australia. Upon accessing the web page the respondents were provided an introduction to the study and were asked to review the informed consent document. The University of Rhode Island Institutional Review Board (URI-IRB) reviewed and approved the two questionnaires and the informed consent document before start of the study. The questionnaires were also pre-tested in a small group of individuals and appropriate modifications were made before start of the study. Upon giving their consent, the respondents completed the electronic survey questionnaire and their responses were stored in a Microsoft Access database. To preserve the anonymity of the respondents, no information related to the respondent except the date of completion of the questionnaire was captured in the database.

Measures: An internet based electronic survey questionnaire instrument was the primary data collection method used in this study. The statements for the questionnaire were adapted from the public hearing notice published by the FDA with a few modifications made to the phraseology as presented by the FDA. Selected questions posed by the FDA were presented as statements and respondents were asked to state their attitude using a five-point Likert scale, ranging from strongly disagree (SDA coded as 1), disagree (DA coded as 2), undecided (UD coded as 3), agree (AG coded as 4) to strongly agree (SAG coded as 5). Respondents were also asked to state their knowledge (poor, moderate, good and very good) of nonprescription regulations, location (Japan, Australia, United Kingdom, United States, Canada and Other) and profession (registered pharmacist, pharmaceutical industry professional, government regulatory agency professional, academic professional and other). Respondents were offered the opportunity to make any additional comments. The respondents were

allowed to choose only one response for each statement. Two questionnaires were developed: one for the United States and a second for all other countries. These questionnaires differed minimally and the great majority of the questions were identical. The sets of statements used in the two questionnaires are presented as an appendix to this article.

The questionnaires were developed as an electronic form for completion by the respondents and were made available over the internet at a website (www.npmsurvey.org) from March to October, 2001 to facilitate unrestricted and convenient global access.

Statistical analyses: Descriptive statistics such as the mean response, the standard error of the mean, the mode response, standard deviation, the sample size and the 95% confidence level of the mean were computed. In addition to descriptive statistics, Chi-square test of independence was performed to understand the relationship between the country of the respondent and variability in their responses. For statistical testing, the five point Likert scale was abridged to a three-point scale resulting in agree, undecided and disagree categories on the response scale.

Using the contingency table constructed for each statement, the value of the Chi-square test statistic was computed. The rejection rule was to reject the null hypothesis (the responses are independent of the respondent's country) if the computed test statistic was greater than 12.59 (standard chi-square value for 5% level of significance and six degrees of freedom).

Results

A total of 473 responses were received from United States, Australia, United Kingdom and Canada. Table 1 provides a detailed summary of the composition and distribution of the responses received based on the profession, country and knowledge of nonprescription regulations of the survey respondents. A substantial majority of all responses (65%) were received from United States whereas the reminder of responses was approximately equally distributed between Australia (10%), UK (12%) and Canada (13%). Response rates of about 17% and 7% were observed for the two cohorts of respondents in the United States and outside United States respectively. Tables 2A to 2C present an overall summary of the responses on each statement and associated descriptive statistics. Results are summarized below according to question content:

Regulatory environment

49% of Americans thought that the current regulatory environment for marketing OTC medicines in the US was inadequate and 41% took the contrary view. Unlike American respondents, a majority of Australians (86%), Britains (59%) and Canadians (70%) stated that the current regulatory environment for marketing OTC medicines in their respective countries was adequate. When asked if the US FDA can learn from different OTC regulatory environments and marketing systems within developed nations, 64% respondents answered in the affirmative. On the same issue, 60% of Australians, 79% of Britains and 89% of Canadians believed their respective regulatory authority could learn from other countries.

An overwhelming majority (80%) of American respondents believed that the US should adopt a regulatory framework that includes an intermediate, pharmacist-

controlled class of nonprescription medicines. Similarly, 85% of Americans opined that US FDA should issue a "guidance for industry" document on the reclassification of prescription products to OTC status describing the nature of the evidence required to substantiate such applications. An implication of this result is that although the OTC standards for safety, effectiveness and labeling are described in 21CFR §330.10(a)(4), it may be useful to delineate such data requirements in a guidance document especially to support an Rx-to-OTC switch petition.

A substantial majority of all respondents (75% of Americans, 78% of Australians, 82% of Britains and 85% of Canadians) endorsed the development of globally acceptable monographs for OTC drug products within the developed world. Contrarily, there was no clearly inferable opinion from the American respondents on the issue of direct-to-consumer marketing of prescription drug products adversely influencing reclassification to OTC status and availability of new OTC drug products as approximately, 31% disagreed, 34% were undecided and 35% agreed.

Role of regulatory agency

When asked if their regulatory agency should actively propose OTC marketing of a drug in the absence of support from the sponsor, the response was varied. American opinion was evenly split with 40% disagreeing, 39% agreeing and 21% being undecided. Roughly two-thirds of the Australian respondents disagreed with this statement, whereas 42% of British respondents agreed and half the Canadians disagreed with this proposal. About 19% Canadians, 21% Americans and 22% Britains remained undecided. Responses were found to be statistically independent of the participant's location in this case. On the related question of their regulatory agency unilaterally

initiating switches of prescription medicines to OTC use, American opinion was unclear with 43% agreeing, 42% disagreeing and 15% being undecided. Roughly 70% of Australians disagreed and 52% of Britains agreed with this idea. A majority of Canadians (45%) rejected this notion.

Criteria for OTC classification

In the US, 33% of respondents thought that the current criteria used by the US FDA in rendering decisions on OTC availability of OTC drug products was adequate, whereas 35% disagreed with this view and 32% remained undecided. This ambivalence reinforces the dissatisfaction of Americans observed earlier with their OTC regulatory framework. On the same issue, 58% of Australians, 46% of Britains and 60% of Canadians believed their respective criterion for decisions on OTC availability to be adequate, but, 13% of Australians, 28% of Britains and 25% of Canadians said they were undecided. These responses were found not to be statistically independent of the participant's location.

The respondents almost unanimously (95% of Americans, 93% of Australians, 98% of Britains and 95% of Canadians) stated that the risks and benefits to individuals and public health should be assessed and weighed in any decision on OTC marketing of drug products. 90% of Americans stated that initiatives to market at least some nontraditional medicines (dietary supplements and nutraceuticals) as regular OTC products by subjecting them to the same rigorous premarketing scientific evaluation and clinical review criteria should be promoted. Also, most respondents added that this is perhaps the most important public health issue in the area of OTC medicines regulation

Suitability of drugs for OTC status and disease conditions for self-medication

The majority of Americans (65%), Britains (70%) and Canadians (68%) stated that chronic illnesses (such as asthma) are not suitable for treatment with OTC products. But, 56% of Australian respondents agreed to the contrary. In Australia, β -agonist inhalation products for asthma are available without a prescription under the pharmacist class of medicines due to which a majority of Australians believed that asthma is suitable for self-medication. A consistent majority across all countries, 59% Americans, 71% Australians, 70% of Britains and 73% of Canadians stated that diseases that require initial diagnosis by a physician (such as hypercholesterolemia) are unsuitable for self-medication. This attitude is in unison with FDA's position that irrespective of the safety profile of the drug molecule, OTC indications for cholesterol-lowering drugs are not appropriate as high cholesterol is a condition that is inherently unsuitable for self-diagnosis and self-medication. Based on this rationale, FDA recently refused to approve OTC status for lovastatin and pravastatin, two cholesterol-lowering medications (2,3). Similarly, a substantial majority of about 75% of respondents from all four countries believed that diseases (such as hypertension) that, if left untreated or are inadequately treated can lead to serious morbidity or mortality are also unsuitable for self-medication.

More than three-quarters of all respondents from each country believed that diuretics should not be made available without a prescription. At least 83% of all respondents from each country disagreed that antihypertensive drugs should be available OTC. Similarly, more than three-quarters (78%) of all respondents from each country believed that oral antidiabetic drugs, and, at least 85% of all respondents from

each country stated that antimicrobials, should not be granted OTC status. The majority of all respondents, 59% Americans, 78% Australians, 61% Britains and 68% of Canadians, did not believe that cholesterol lowering drugs should become nonprescription medicines. 69% of Australians, 46% of Britains and 54% of Canadians disagreed with granting OTC status for treatments for osteoporosis (including its prevention), whereas, a majority of Americans (48%) agreed with this proposal. Opinion was diverse on the idea of removing the prescription requirement for oral contraceptives. More Americans disagreed (45%) than that agreed (42%) with this proposal. 46% Australians disagreed versus 40% Australians that agreed with OTC status for oral contraceptives. 57% of British respondents agreed, whereas, 49% of Canadians disagreed with oral contraceptives being given OTC status.

Consumer understanding and behavior

A majority of respondents from all countries, 55% Americans, 55% Australians, 63% Britains and 54% Canadians, rejected the idea that rational selection of treatment regimens by consumers may be ensured when prescription and OTC therapies coexist for a certain disease. Similarly, more than 80% of respondents from all countries thought that patients do not know the best ways to treat their illnesses in an environment with coexisting prescription and OTC therapies for a certain disease. At least 63% of respondents from all countries thought that prevention claims for OTC medicines would encourage ill-advised behavior (such as ignoring smoking cessation and dietary discretion while using an OTC cholesterol-lowering drug, if it were available) among consumers.

Approval of new OTC medicines

When asked if the first drug to enter the OTC market should be the “best” drug in terms of benefit-to-risk ratio within a therapeutic class, a majority of respondents concurred. Almost half (49%) of Americans, about 56% Australians, about two-thirds (67%) of Britains and 58% of Canadians were in agreement with the above statement. In United States, this is not true as the order of availability of new OTC medicines to the general public is decided by the sponsor’s willingness to switch and the FDA has no role in this decision. As discussed earlier, the issue of regulatory agencies initiating and pursuing switch proposals in the absence of support from the sponsor is critical in this context. A majority of the respondents from all countries (46% Americans, 60% Australians, 63% Britains and 50% Canadians) agreed that the availability of a “better” OTC product in terms of efficacy or safety should affect the status of products already in the OTC market for treatment of the same condition within a therapeutic class. Additionally, about two-thirds of the respondents (66% Americans, 67% Australians, 69% Britains and 65% Canadians) believed that when newer nonprescription products become available within a therapeutic class, older therapies that may provide less benefit or more risk should be either removed from the market or their labeling should be revised. These observations must be interpreted cautiously as the decision to remove older OTC medicines upon availability of newer OTC medicines must be considered on a case specific basis. In some cases removal of an OTC medicine (as in the case of phenylpropanolamine in the United States) may be the right course due to public health reasons. However, attempts to extend such a policy universally may be imprudent as individuals do not show a uniform pharmacological response to any medicine and it is

necessary to allow for a choice of pharmacological therapies being available to individuals.

There was variability among responses on the issue of direct-to-OTC marketing (a new chemical entity (NCE) is directly granted OTC status without being first marketed as a prescription product for some duration of time). 46% of Americans, 51% of Australians, 78% of Britains and 36% of Canadians agreed with the principle of direct-to-OTC marketing, whereas, 37% of Americans, 33% of Australians, 20% of Britains and 49% of Canadians disagreed. The responses on this statement were found not to be statistically independent of the country as each regulatory agency has taken a different position on this matter. Also, an opinion held by most health professionals is that a drug's safety profile cannot be understood based solely on controlled clinical trails during development and surveillance during real-world clinical practice is necessary.

Discussion

Literature in this scientific discipline does not widely document the use of internet, despite its obvious and well-known advantages, for administering a survey. This study demonstrates the utility of electronic communication in the rapid and effective completion of a global survey. Also, the electronic survey instrument is presented as an efficient alternative to traditional questionnaire-by-mail survey technique.

As with any study, this study is also subject to limitations and the results must only be interpreted within the context of any such limitations. Some noteworthy limitations are: (a) the phraseology of the questionnaire may not ensure consistent

comprehension by all respondents, (b) responses are influenced by the inherent biases of the respondents (c) respondents were forced to choose only one response on the five-point Likert scale that is closest to, but not necessarily, their true opinion (d) the participants did not have the opportunity to qualify their responses (e) the study sample population may not accurately represent the overall population (f) normal distribution of responses that is not fully accurate was assumed in the estimation of descriptive statistics. Additionally some respondents commented that their opinion could not be completely captured using only a five-point scale. Despite the limitations, these results are useful to discern the attitudes of certain stakeholders on regulation of nonprescription medicines. This assertion is reinforced, as the study is exploratory in nature and was not designed to test any specific hypotheses. Moreover, the absence of any information in the global context related to these important issues accentuates the significance of these results.

Foreign respondents outnumbered American participants in stating that their regulatory agency can learn from other nations, despite the observation that their level of satisfaction with their regulatory systems was greater than that for Americans. On statement 1 (current regulatory environment for marketing nonprescription medicines (NPM) in the US is adequate) and statement 2 (the US FDA can learn from different nonprescription medicine regulatory environments and marketing systems within other developed nations), statistical analysis showed that nature of the responses was not independent of the country of the participant. This dependence of responses on the country may be attributed to the differences in regulatory frameworks within the four countries. The endorsement of an intermediate, pharmacist-controlled class of

nonprescription medicines by the American respondents is very significant and this contentious matter has been debated for a long time (4,5,6). Although the respondent population does not include all stakeholders, it can be inferred that there is strong support for such a proposal amongst an important subsection of stakeholders. However, it is necessary to evaluate the support for an intermediate-class of OTC drugs amongst a broader population of stakeholders as this study focussed only on pharmacists and academicians. Also, it may be reasoned that this is a potential improvement to the US regulatory system on which American respondents may have based their earlier response.

Presently, the US OTC monograph system is unique among the four countries wherein an OTC product may be marketed without pre-market approval if compliance with an approved OTC monograph is ensured. Such an initiative when expanded to other countries would benefit the general public and the pharmaceutical industry as best practices related to OTC regulation from across the developed world can be integrated resulting in an efficient OTC product development and approval system. Statistical analysis showed that the responses on statement 5 (on the US questionnaire, "the US FDA should be more active in unilaterally initiating switches of prescription medicines to nonprescription use") were found not to be independent of the participant's location. Although, the inferential The Chi-square test statistics for statements 4 and 5 in the US questionnaire (11.39 and 14.81 respectively) although minimally different from the critical value for rejection (12.59) led to differing statistical inferences. Overall, there is ambivalence on the issue of regulatory agencies initiating and pursuing switch proposals in the absence of support from the sponsor. This observation is timely and

important in the context of proposed OTC status for second-generation, non-sedating antihistamines in the United States (7,8). Although, this topic has substantial legal complexity and experts in drug law did not participate in this study, it is important for the FDA to consider the opinion of pharmacists and academicians in formulating its regulatory policy on OTC status for non-sedating antihistamines.

It is important to note that responses on statements related to suitability of disease conditions and drugs for self-medication were found to be statistically independent of the country in all but, two cases. The United States has only one class of nonprescription medicines whereas Australia, United Kingdom and Canada have two classes of nonprescription medicines (one that requires consultation with a pharmacist in a pharmacy before purchase and the other that may be purchased anywhere). It has been argued that the existence of the pharmacist-controlled class of nonprescription medicines offers a more efficient approach to manage the risk/benefit ratio associated with potent nonprescription medicines and ensures their safe use. If this hypothesis were true, it is reasonable to expect that the responses of participants from countries with a pharmacist-controlled class of nonprescription medicines might possibly be different from those in United States. However, the results show this trend only in two of the ten statements. Also, a proportion of all respondents stated that their responses on above statements might have been different if a pharmacist-class of nonprescription medicines was available and pharmacist intervention can be frequently exercised. Hence, it is unclear if a majority of all respondents believe that most of the diseases or drug classes discussed above are unsuitable for self-medication even if a pharmacist-controlled class of nonprescription medicines were available. Two limitations of this

study, the phraseology of the questionnaire not possibly ensuring consistent comprehension by all respondents and the participants not having the opportunity to qualify their responses, are particularly important in this context. It is necessary that subsequent studies designed to specifically test hypotheses such as these must be conducted for an accurate assessment.

Recently, dietary supplements have witnessed a rapid growth in usage (9,10,11,12) and there has been a vocal expression of concern among the professional community over the safety and efficacy of these products and this overall opinion is aligned with the views of the majority of the scientific and medical community (13,14,15,16,17). The responses observed on regulation of dietary supplements imply that such products presently regulated as per the Dietary Supplement Health and Education Act (DSHEA) of 1994 need to be comprehensively reviewed and fundamental changes must be made to the regulatory framework. Observations on the subject of consumer understanding and behavior related to nonprescription medicines indicate that the respondents believe that consumers possess neither the knowledge nor the commitment to correctly select and safely use OTC medicines without being assisted by a learned intermediary. It is vitally important for consumers to responsibly use OTC medicines and effective education of the general public must be accomplished. The significance of these observations is augmented as it is expected that attempts to make potent prescription medicines available without a prescription will increase in the future.

Conclusion

This study demonstrates the rapid and effective administration of an electronic survey questionnaire to a global audience with the objective of developing answers to questions that the US FDA posed on the subject of nonprescription medicine regulations. It can be inferred that relative to Australian, British and Canadian participants more American respondents regard their regulatory framework for OTC medicines as inadequate. Results suggest that potential improvements to the US regulatory framework can include creation of an intermediate, pharmacist-controlled class of OTC medicines, delineation of data requirements in a guidance document to support a switch petition, regulation of nontraditional medicines (dietary supplements and nutraceuticals) based also on current OTC standards of pre-market demonstration of safety and efficacy, and, the development of global OTC monographs.

Responses from all four countries show ambivalence towards the role of regulatory agencies in initiating switches or unilaterally switching medicines to nonprescription status without the sponsor's support. Respondents unanimously stated that risks and benefits to individuals and public health must be the paramount criterion in rendering decisions on availability of new OTC medicines. A substantial majority of all respondents believed that chronic illnesses (such as asthma), diseases that require initial diagnosis by a physician (such as hypercholesterolemia) and diseases such as hypertension are unsuitable for self-diagnosis and self-medication. Respondents also firmly believed that diuretics, antihypertensive drugs, oral antidiabetic drugs, antimicrobials, cholesterol-lowering drugs, osteoporosis medications and oral contraceptives are not appropriate for self-medication. However, the study results do

not help in understanding if these attitudes might change if a pharmacist-class of nonprescription medicines were available. Respondents also thought that the consumers do not possess the knowledge or ability to ensure responsible use of potent nonprescription medicines without the help of a learned intermediary.

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Appendix

List of statements in the questionnaire for US respondents

1. Current regulatory environment for marketing nonprescription medicines (NPM) in the US is adequate.
2. The US FDA can learn from different nonprescription medicine regulatory environments and marketing systems within other developed nations.
3. US should adopt a regulatory framework that includes an intermediate, pharmacist-controlled class of nonprescription medicines (i.e. behind-the-counter medicines).
4. The US FDA should actively propose nonprescription marketing of a prescription drug in the absence of support from the drug manufacturer (sponsor).
5. The US FDA should be more active in unilaterally initiating switches of prescription medicines to nonprescription use.
6. Current criteria used by the US FDA in rendering decisions on availability of nonprescription drug products is adequate.
7. The following types of diseases/illnesses are suitable for treatment with nonprescription drug products:

- a. Chronic illnesses (such as asthma)
 - b. Diseases that require initial diagnosis by a physician (such as hypercholesterolemia, i.e. high cholesterol)
 - c. Diseases (such as hypertension) that, if left untreated or are inadequately treated can lead to serious morbidity or mortality
8. The following are specific classes of medicines that are not currently marketed as nonprescription medicines that should be available without a prescription:
- a. Diuretics
 - b. Antihypertensive drugs
 - c. Cholesterol lowering drugs
 - d. Oral antidiabetic drugs
 - e. Treatments for osteoporosis (including its prevention)
 - f. Antimicrobials
 - g. Oral contraceptives
9. Rational selection of treatment regimens by consumers may be ensured when there are coexisting prescription and nonprescription therapies for a certain disease.
10. Patients know the best ways to treat their illnesses in an environment with coexisting prescription and nonprescription therapies for a certain disease.

11. The risks and benefits to individuals and public health should be assessed and weighed in any decision on nonprescription marketing of drug products (for example, the potential benefits of nonprescription antimicrobial agents with the potential risks to society at large of the development of resistant organisms).
12. Prevention claims for nonprescription medicines encourage ill-advised behavior (for example, use of an nonprescription cholesterol lowering drug would allow patients to ignore other needed interventions such as smoking cessation, dietary discretion and management of other risk factors).
13. Within a therapeutic class, the first drug to enter the nonprescription market should be the “best” drug in terms of the benefit-to-risk ratio.
14. Within a therapeutic class, the availability of a “better” nonprescription product in terms of efficacy or safety should affect the status of products already on the nonprescription market for treatment of the same condition.
15. When newer nonprescription products become available within a therapeutic class, older therapies that may provide less benefit or more risk should be either removed from the market or their labeling should be revised.
16. Initiatives to market at least some nontraditional medicines (dietary supplements, vitamins, nutraceuticals and other traditional medicines) as regular OTC drug products by subjecting them to the same rigorous premarketing scientific evaluation and clinical review criteria should be promoted.

17. Direct-to-consumer marketing of prescription drug products adversely influences reclassification to OTC status and availability of new OTC drug products.
18. Initiatives to develop and establish globally acceptable monographs for nonprescription drug products, at least, within the developed world should be promoted.
19. The US FDA should issue a "Guidance for Industry" document on the reclassification of prescription products to OTC status describing the nature of evidence required to substantiate such applications.
20. Assuming a new chemical entity meets all regulatory requirements necessary for nonprescription classification, it should still be marketed as prescription medicine for a specified duration before reclassification to nonprescription status may be considered.

List of statements in the questionnaire for outside US respondents

1. Current regulatory environment for marketing nonprescription medicines (NPM) in your country is adequate.
2. Your country can learn from different nonprescription medicine regulatory environments and marketing systems within other developed nations.
3. The relevant regulatory Agency in your country should actively propose nonprescription marketing of a prescription drug in the absence of support from the drug manufacturer (sponsor).

4. The relevant regulatory Agency in your country should be more active in unilaterally initiating switches of prescription medicines to nonprescription use.
5. Current criteria used by the relevant regulatory Agency in your country in rendering decisions on availability of nonprescription drug products is adequate.
6. The following types of diseases/illnesses are suitable for treatment with nonprescription drug products:
 - a. Chronic illnesses (such as asthma)
 - b. Diseases that require initial diagnosis by a physician (such as hypercholesterolemia, i.e. high cholesterol)
 - c. Diseases (such as hypertension) that, if left untreated or are inadequately treated can lead to serious morbidity or mortality
7. The following are specific classes of medicines that are not currently marketed as nonprescription medicines that should be available without a prescription:
 - a. Diuretics
 - b. Antihypertensive drugs
 - c. Cholesterol lowering drugs
 - d. Oral antidiabetic drugs
 - e. Treatments for osteoporosis (including its prevention)
 - f. Antimicrobials

g. Oral contraceptives

8. Rational selection of treatment regimens by consumers may be ensured when there are coexisting prescription and nonprescription therapies for a certain disease.
9. Patients know the best ways to treat their illnesses in an environment with coexisting prescription and nonprescription therapies for a certain disease.
10. The risks and benefits to individuals and public health should be assessed and weighed in any decision on nonprescription marketing of drug products (for example, the potential benefits of nonprescription antimicrobial agents with the potential risks to society at large of the development of resistant organisms).
11. Prevention claims for nonprescription medicines encourage ill-advised behavior (for example, use of a nonprescription cholesterol lowering drug would allow patients to ignore other needed interventions such as smoking cessation, dietary discretion and management of other risk factors).
12. Within a therapeutic class, the first drug to enter the nonprescription market should be the “best” drug in terms of the benefit-to-risk ratio.
13. Within a therapeutic class, the availability of a “better” nonprescription product in terms of efficacy or safety should affect the status of products already on the nonprescription market for treatment of the same condition.

14. When newer nonprescription products become available within a therapeutic class, older therapies that may provide less benefit or more risk should be either removed from the market or their labeling should be revised.
15. Initiatives to develop and establish globally acceptable monographs for nonprescription drug products, at least, within the developed world should be promoted.
16. Assuming a new chemical entity meets all regulatory requirements necessary for nonprescription classification, it should still be marketed as prescription medicine for a specified duration before reclassification to nonprescription status may be considered.

Table 1: Distribution of survey respondents classified by profession, country and knowledge of nonprescription regulations

Profession										
	US		Australia		UK		Canada		All countries	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Reg Pharm	140	45.16	32	71.11	30	54.55	22	34.92	224	47.36
Pharm Ind Prof	4	1.29	4	8.89	1	1.82	5	7.94	14	2.96
Govt RA Prof	0	0.00	1	2.22	0	0.00	3	4.76	4	0.85
Acad Prof	155	50.00	7	15.56	23	41.82	30	47.62	215	45.45
Other	11	3.55	1	2.22	1	1.82	3	4.76	16	3.38
Total	310	100.00	45	100.00	55	100.00	63	100.00	473	100.00
% of Respondents per country	65.54		9.51		11.63		13.32		100.00	
Knowledge of nonprescription regulations										
	US		Australia		UK		Canada		All countries	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Poor	45	14.52	2	4.44	10	18.18	4	6.35	61	12.90
Moderate	133	42.90	4	8.89	19	34.55	13	20.63	169	35.73
Good	106	34.19	14	31.11	14	25.45	22	34.92	156	32.98
Very good	26	8.39	25	55.56	12	21.82	24	38.10	87	18.39
Total	310	100.00	45	100.00	55	100.00	63	100.00	473	100.00

Table 2A: Summary of responses to survey statements and descriptive statistics

Statement	Country	Response (%)					Descriptive statistics							
		SDA	DA	UD	AG	SAG	Mean	SE	Mode	SD	N	CI(95.0 %)	Chi-sq	Sign.
1	US	6.82	42.21	9.42	40.26	1.30	2.87	0.06	2	1.07	308	0.12	45.90	yes
	Aus.	0.00	8.89	4.44	71.11	15.56	3.93	0.11	4	0.75	45	0.23		
	UK	9.26	22.22	9.26	53.70	5.56	3.18	0.16	4	1.22	55	0.33		
	Can.	3.17	19.05	7.94	65.08	4.76	3.49	0.12	4	0.97	63	0.24		
2	US	1.30	10.06	24.03	53.57	10.71	3.63	0.05	4	0.86	307	0.10	40.01	yes
	Aus.	8.89	24.44	6.67	51.11	8.89	3.27	0.18	4	1.19	45	0.36		
	UK	0.00	9.26	12.96	62.96	16.67	3.85	0.10	4	0.80	55	0.22		
	Can.	1.59	4.76	4.76	73.02	15.87	3.97	0.09	4	0.74	63	0.19		
3	US	3.57	6.17	10.06	38.96	41.23	4.08	0.06	5	1.04	308	0.12	none	none
4(3)	US	10.71	29.22	21.10	30.84	7.79	2.96	0.07	4	1.16	307	0.13	11.39	no
	Aus.	24.44	40.00	11.11	20.00	4.44	2.40	0.18	2	1.19	45	0.36		
	UK	7.41	29.63	22.22	37.04	5.56	3.04	0.14	4	1.09	55	0.29		
	Can.	15.87	31.75	19.05	23.81	7.94	2.71	0.15	2	1.26	63	0.32		
5(4)	US	8.44	33.44	14.94	36.69	6.49	2.99	0.07	4	1.14	308	0.13	14.81	yes
	Aus.	15.56	53.33	4.44	22.22	4.44	2.47	0.17	2	1.14	45	0.34		
	UK	5.56	29.63	14.81	48.15	3.70	3.14	0.14	4	1.06	55	0.29		
	Can.	7.94	36.51	15.87	28.57	11.11	2.98	0.15	2	1.20	63	0.30		
6(5)	US	3.25	32.14	30.84	31.82	1.62	2.96	0.05	2	0.92	307	0.10	25.83	yes
	Aus.	4.44	24.44	13.33	57.78	0.00	3.24	0.14	4	0.98	45	0.29		
	UK	3.70	24.07	27.78	44.44	1.85	3.16	0.12	4	0.94	55	0.25		
	Can.	3.17	11.11	25.40	55.56	4.76	3.48	0.11	4	0.88	63	0.22		
7A(6A)	US	25.65	39.29	5.84	26.30	1.95	2.39	0.07	2	1.19	305	0.13	17.32	yes
	Aus.	8.89	31.11	4.44	48.89	6.67	3.13	0.17	4	1.20	45	0.36		
	UK	24.07	46.30	3.70	20.37	5.56	2.33	0.16	2	1.25	55	0.34		
	Can.	20.63	47.62	7.94	17.46	4.76	2.33	0.14	2	1.18	63	0.30		
7B(6B)	US	20.13	38.96	8.77	27.92	2.92	2.54	0.07	2	1.19	304	0.13	9.20	no
	Aus.	20.00	51.11	8.89	20.00	0.00	2.29	0.15	2	1.01	45	0.30		
	UK	14.81	51.85	1.85	20.37	9.26	2.47	0.17	2	1.32	55	0.36		
	Can.	20.63	52.38	4.76	20.63	0.00	2.22	0.13	2	1.05	63	0.27		
7C(6C)	US	30.52	44.16	6.49	13.31	3.90	2.15	0.06	2	1.12	303	0.13	4.60	no
	Aus.	24.44	57.78	8.89	4.44	4.44	2.07	0.14	2	0.96	45	0.29		
	UK	20.37	57.41	1.85	16.67	1.85	2.13	0.14	2	1.09	55	0.29		
	Can.	26.98	46.03	7.94	12.70	4.76	2.18	0.14	2	1.16	63	0.29		

Table 2B: Summary of responses to survey statements and descriptive statistics

		Response (%)					Descriptive statistics							
Staten ent	Country	SDA	DA	UD	AG	SAG	Mean	SE	Mode	SD	N	CI(95.0 %)	Chi-sq	Sign.
8A(7A)	US	26.30	49.03	5.84	15.91	1.62	2.16	0.06	2	1.05	304	0.12	7.70	no
	Aus.	35.56	51.11	8.89	2.22	2.22	1.84	0.12	2	0.85	45	0.26		
	UK	35.19	48.15	7.41	11.11	0.00	1.94	0.12	2	0.93	55	0.25		
	Can.	28.57	49.21	9.52	12.70	0.00	2.06	0.11	2	0.95	63	0.24		
8B(7B)	US	35.39	48.05	4.55	9.74	0.97	1.91	0.05	2	0.94	304	0.11	3.14	no
	Aus.	37.78	51.11	4.44	6.67	0.00	1.8	0.12	2	0.81	45	0.24		
	UK	33.33	50.00	9.26	9.26	0.00	1.95	0.12	2	0.89	55	0.24		
	Can.	33.33	52.38	6.35	7.94	0.00	1.89	0.10	2	0.84	63	0.21		
8C(7C)	US	20.78	38.64	8.44	27.60	3.57	2.54	0.07	2	1.20	305	0.14	7.01	no
	Aus.	20.00	57.78	4.44	15.56	2.22	2.22	0.15	2	1.02	45	0.31		
	UK	24.07	37.04	9.26	25.93	5.56	2.52	0.17	2	1.26	55	0.34		
	Can.	19.05	49.21	9.52	17.46	4.76	2.39	0.14	2	1.13	63	0.28		
8D(7D)	US	38.96	44.81	6.49	7.47	0.97	1.85	0.05	2	0.91	304	0.10	6.43	no
	Aus.	31.11	55.56	2.22	8.89	2.22	1.96	0.14	2	0.95	45	0.29		
	UK	35.19	55.56	1.85	9.26	0.00	1.85	0.11	2	0.85	55	0.23		
	Can.	33.33	44.44	11.11	11.11	0.00	2.00	0.12	2	0.95	63	0.24		
8E(7E)	US	7.14	30.19	13.31	44.48	3.90	3.08	0.06	4	1.09	305	0.12	20.63	yes
	Aus.	15.56	53.33	11.11	17.78	2.22	2.38	0.15	2	1.03	45	0.31		
	UK	9.26	37.04	12.96	38.89	3.70	2.90	0.15	4	1.13	55	0.30		
	Can.	19.05	34.92	6.35	36.51	3.17	2.69	0.15	4	1.24	63	0.31		
8F(7F)	US	58.44	28.25	7.14	3.57	1.30	1.59	0.05	1	0.87	304	0.10	7.37	no
	Aus.	46.67	37.78	4.44	8.89	0.00	1.75	0.13	1	0.92	44	0.28		
	UK	40.74	44.44	3.70	12.96	0.00	1.89	0.13	2	0.98	55	0.26		
	Can.	57.14	33.33	3.17	6.35	0.00	1.58	0.10	1	0.84	63	0.21		
8G(7G)	US	14.61	30.52	12.01	33.44	8.44	2.90	0.07	4	1.25	305	0.14	5.49	no
	Aus.	8.89	37.78	13.33	33.33	6.67	2.91	0.17	2	1.16	45	0.35		
	UK	5.56	25.93	11.11	44.44	12.96	3.27	0.16	4	1.24	55	0.33		
	Can.	19.05	30.16	11.11	33.33	6.35	2.78	0.16	4	1.28	63	0.32		
9(8)	US	12.34	42.53	19.81	20.13	2.60	2.57	0.06	2	1.04	300	0.12	5.91	no
	Aus.	15.56	40.00	15.56	26.67	2.22	2.6	0.16	2	1.12	45	0.34		
	UK	16.67	46.30	24.07	11.11	0.00	2.21	0.13	2	0.98	55	0.26		
	Can.	14.29	39.68	19.05	23.81	3.17	2.61	0.13	2	1.10	63	0.28		

Table 2C: Summary of responses to survey statements and descriptive statistics

Statement	Country	Response (%)					Descriptive statistics							
		SDA	DA	UD	AG	SAG	Mean	SE	Mode	SD	N	CI(95.0 %)	Chi-sq	Sign.
10(9)	US	31.49	48.70	10.71	4.87	0.65	1.91	0.05	2	0.83	297	0.10	1.31	no
	Aus.	33.33	48.89	11.11	4.44	0.00	1.86	0.12	2	0.80	44	0.24		
	UK	18.52	66.67	9.26	3.70	0.00	1.90	0.10	2	0.75	55	0.20		
	Can.	28.57	53.97	9.52	7.94	0.00	1.96	0.10	2	0.84	63	0.21		
11(10)	US	0.65	0.32	2.27	36.04	59.09	4.55	0.04	5	0.63	303	0.07	4.62	no
	Aus.	4.44	0.00	2.22	44.44	48.89	4.33	0.13	5	0.90	45	0.27		
	UK	0.00	0.00	1.85	51.85	46.30	4.36	0.10	4	0.80	55	0.22		
	Can.	1.59	0.00	1.59	30.16	65.08	4.52	0.11	5	0.90	63	0.23		
12(11)	US	2.60	21.10	10.06	50.97	13.96	3.53	0.06	4	1.06	304	0.12	2.66	no
	Aus.	4.44	17.78	8.89	40.00	28.89	3.71	0.17	4	1.20	45	0.36		
	UK	1.85	18.52	16.67	44.44	18.52	3.52	0.15	4	1.15	55	0.31		
	Can.	3.17	17.46	12.70	47.62	19.05	3.61	0.13	4	1.08	63	0.27		
13(12)	US	6.82	27.27	15.26	40.58	8.77	3.17	0.07	4	1.14	304	0.13	11.94	no
	Aus.	6.67	22.22	15.56	42.22	13.33	3.33	0.17	4	1.17	45	0.35		
	UK	5.56	9.26	18.52	48.15	18.52	3.58	0.15	4	1.17	55	0.32		
	Can.	3.17	17.46	20.63	46.03	12.70	3.47	0.13	4	1.03	63	0.26		
14(13)	US	3.57	31.17	17.21	39.94	6.49	3.15	0.06	4	1.06	303	0.12	11.62	no
	Aus.	2.22	31.11	6.67	53.33	6.67	3.31	0.15	4	1.06	45	0.32		
	UK	0.00	18.52	18.52	57.41	5.56	3.43	0.13	4	0.98	55	0.26		
	Can.	4.76	22.22	22.22	44.44	6.35	3.25	0.13	4	1.03	63	0.26		
15(14)	US	4.22	19.16	9.42	53.90	12.01	3.51	0.06	4	1.07	304	0.12	11.25	no
	Aus.	6.67	22.22	4.44	55.56	11.11	3.42	0.17	4	1.16	45	0.35		
	UK	0.00	14.81	16.67	61.11	7.41	3.55	0.12	4	0.96	55	0.26		
	Can.	3.17	12.70	19.05	55.56	9.52	3.56	0.11	4	0.95	63	0.24		
16	US	1.30	3.25	4.22	38.64	51.30	4.37	0.05	5	0.82	304	0.09	none	none
17	US	3.25	27.92	32.79	27.60	7.47	3.08	0.06	3	0.99	305	0.11	none	none
18(15)	US	1.62	8.44	12.99	61.36	14.29	3.79	0.05	4	0.85	304	0.10	4.53	no
	Aus.	2.22	4.44	15.56	42.22	35.56	4.04	0.14	4	0.95	45	0.29		
	UK	0.00	5.56	12.96	53.70	27.78	3.96	0.13	4	0.96	55	0.26		
	Can.	6.35	1.59	6.35	53.97	31.75	4.03	0.12	4	1.02	63	0.26		
19	US	0.65	0.32	12.34	62.66	22.08	4.07	0.04	4	0.65	302	0.07	none	none
20(16)	US	3.25	33.77	14.94	34.42	12.01	3.18	0.07	4	1.13	303	0.13	24.19	yes
	Aus.	11.11	22.22	15.56	31.11	20.00	3.27	0.19	4	1.32	45	0.40		
	UK	3.70	16.67	1.85	53.70	24.07	3.70	0.16	4	1.21	55	0.33		
	Can.	12.70	36.51	14.29	30.16	6.35	2.81	0.15	2	1.19	63	0.30		

Table 2D: Description of legends for Tables 2A through 2C

Response (%)	Indicates the % of all study respondents with that view
SDA	Strongly disagree
DA	Disagree
UD	Undecided
AG	Agree
SAG	Strongly agree
Descriptive statistics	
Mean	The mean response
SE	Standard error associated with the mean response
Mode	The response with the highest frequency
SD	Standard deviation associated with the responses
N	Sample size or total number of respondents
CI(95.0%)	95% confidence interval around the mean response
Chi-sq.	Value of the chi-square test statistic computed as described in the text of the article
Sign.	Results of the chi-square test describing the statistical significance or lack thereof

MANUSCRIPT VIII

ATTITUDES AND OPINIONS TOWARDS REGULATORY ASPECTS OF NONPRESCRIPTION MEDICINES: PART 2

Abstract

The first part of this investigation developed and described quantitative answers to questions that FDA has posed through the administration of an electronic survey questionnaire. The goal of this part was to qualitatively probe these issues further by conducting telephone interviews with key opinion leaders in the United States, Canada, the United Kingdom and Australia. This study aimed to extend the earlier effort and gain additional insight into issues described above and explored the opinions of thirty six key opinion leaders and stakeholders in the area of OTC medicines regulation from the United States, United Kingdom, Australia and Canada. Results suggest that potential improvements to the US regulatory framework can include creation of an intermediate, pharmacist-controlled class of OTC medicines, delineation of data requirements in a guidance document to support a switch petition, regulation of nontraditional medicines (dietary supplements and nutraceuticals) also as per current OTC standards of pre-market demonstration of safety and efficacy, and, the development of global OTC monographs. Responses showed support for regulatory agencies to unilaterally switch drug products and such decisions to be based only on the overall public health benefit considerations.

Introduction

As part of examining its overall approach to regulating over-the-counter (OTC) drug products the US Food and Drug Administration (FDA) has conducted a public hearing to solicit information from interested persons such as scientists, professional groups and consumers (1). The FDA listed specific questions related to regulatory aspects of OTC drug products upon which it requested comments of all interested groups (such as pharmacists, academicians, physicians, consumers and the pharmaceutical industry).

Part one of this investigation developed and described quantitative answers to questions that FDA has posed (on issues such as the OTC regulatory environment, role of regulatory agency in Rx-to-OTC switches, criteria for OTC classification, suitability of drugs for OTC status and disease conditions for self-medication, consumer behavior and understanding of OTC medicines and the approval of new OTC medicines) developed through the administration of an electronic survey questionnaire. The goal of this part was to qualitatively probe these issues further by conducting telephone interviews with key opinion leaders in the United States, Canada, the United Kingdom and Australia. This study aimed to extend the earlier effort and gain additional insight into issues described above.

Methodology

Measures: A telephone interview survey questionnaire instrument was the primary data collection method used in this study. Also, to obtain a broad spectrum of views, data collected from the public statements of some key opinion leaders in the area of OTC regulation have been used.

Study participants: Requests for participation in the study were forwarded by email or telephone to individuals or organizations with established expertise or interest in the area of nonprescription medicines in the United States, United Kingdom, Canada and Australia. The group of individuals or organizations requested to participate was carefully selected to obtain a broad spectrum of views on OTC medicines and their regulation.

Survey interview: Participants who agreed for the telephone interviews were provided an introduction to the study and explained the informed consent document. The University of Rhode Island Institutional Review Board (URI-IRB) reviewed and approved the questions and the informed consent document before start of the study. Upon giving their consent, all the participants were interviewed by the author. Participants were also requested to grant permission for recording the interview for review and transcription purposes by the author only. Participants were assured that their identity and individual responses will be kept anonymous and that only collective data from the interviews will be publicly discussed. Hence, table 1 describes the nature of the participants only in general terms without specific information. The statements for the interview survey questionnaire were adapted from the public hearing notice published by the FDA with a few modifications made to the phraseology as presented by the FDA. Selected questions posed by the FDA were presented as statements during the interview and respondents were asked to state their opinion. The format of the interview was free flowing and the participants were allowed to respond without any restrictions. The set of statements used in the interviews is appended to this article.

Data analysis: Data collected through the interviews and the public statements was pooled and qualitatively examined to discern prominent observations and trends. An attempt to make inferences helpful towards formulation of rational regulatory policy was also made.

Results

The opinions of thirty-six stakeholders from United States, Australia, United Kingdom and Canada have been collected. The nature and composition of the participants interviewed for this study is presented in table 1. Additionally, table 2 presents a description of the participants whose publicly stated positions on OTC medicines have been used in this study. Some important stakeholders like American Association of Health Plans, National Association of Chain Drug Stores in the US, National Organization for Women and American Association of Retired Persons (AARP) did not respond to the authors interview requests. The Canadian Association of Chain Drug Stores (CACDS) stated that they do not have an official position on this matter. Also, attempts to interview key members of the US House of Representatives and US Senate in the area of healthcare delivery were not fruitful. A majority of the participants (72%) were from United States, representation from UK (11%) and Canada (11%) was equal and the reminder of participants was from Australia (6%). Results have been summarized below according to the nature of the question content.

Regulatory environment

When asked if the regulatory environment for nonprescription medicines was adequate and if learning from other regulatory models can be gained, responses of the participants varied widely. Respondents who thought the regulatory systems were

adequate cited public health and safety as being the underlying criterion for OTC status, the multi-tier scheduling system in Australia allowed better balance between access and safety and the OTC monograph model of product approval in the US was built on strong scientific foundation as reasons. Others disagreed saying that, there was an aggressive thrust towards deregulation by the industry at the risk of public health, the growing demand for counseling and education for nonprescription medicines was unmet, over-regulation was observed where self-regulation could have been adequate, the US Food, Drug & Cosmetic Act does not clearly define an OTC product and FDA does not have adequate resources to regulate OTC medicines.

The American Medical Association (AMA represents physicians), Consumer Health Products Association (CHPA represents manufacturers of nonprescription medicines in the USA) and the Pharmaceutical Research and Manufacturers of America (PhRMA represents research-based pharmaceutical and biotechnology companies in the USA) stated that the existing regulatory model for nonprescription medicines in the United States was adequate and satisfactory due to the success observed since the implementation of OTC Drug Review in the early seventies. Mr. Peter Hutt, a food and drug lawyer who led the FDA's OTC review in the seventies opined that the current priority attached to regulating OTC medicines within the Agency is inadequate and greater importance needs to be placed on this matter. He stated that the present OTC division must be elevated to an office within FDA's organizational hierarchy. He also stated that the unfinished monographs in certain therapeutic areas must be finalized. Mr. Pinco and Mr. Steinberg, two food and drug lawyers also agreed with this view of bringing incomplete monographs to final status.

The views of the participants on the utility of a pharmacist-controlled class of nonprescription medicines were wide-ranging. Almost all respondents interviewed said that the US would benefit from an intermediate class of OTC medicines, but, there were differences in how such an intermediate class was envisioned. However, most respondents said that the creation of such a class of drugs in the US is unlikely due to political reasons. Respondents from Australia, Canada and United Kingdom where such a class of OTC medicines already exists stated that this class facilitates better management of risk and benefit in case of nonprescription medicines. National Community Pharmacist's Association (NCPA) and American Pharmacist's Association (APhA) strongly supported an intermediate class of medicines. Specifically, the NCPA supported a transitional class of medicines that can serve as a bridge between prescription and OTC medicines. The NCPA also stated that the Controlled Substances Act allows for a C-5 category that is sold only under a pharmacist's supervision or by prescription. The APhA also suggested that in some states there are collaborative practice agreements between states and manufacturers allowing limited prescriptive authority for pharmacists. Dr. Wolfe, a physician and consumer advocate and the Women's Health Network also supported the utility of a third class of pharmacist dispensed OTC medicines.

The CHPA and AMA opposed the establishment of a behind-the-counter class of medicines. They cited the study "Nonprescription Drugs: Value of a pharmacist controlled class has yet to be demonstrated" conducted by the US Congress' General Accounting Office as evidence for their position. They asserted that this concept restricts access and has been rejected by the FDA.

A substantial majority of the respondents interviewed stated that direct-to-consumer advertising of prescription pharmaceuticals does not affect the reclassification of those products to OTC status. Also, they strongly endorsed a proposal to create global OTC monographs so that the scientific basis and knowledge used in approval of OTC products may be efficiently shared across nations. Respondents also supported the issuance of a guidance document prepared by the FDA for sponsors describing the nature and kind of evidence required in switch petitions.

Role of regulatory agency

When asked if their regulatory agency should actively and unilaterally propose OTC marketing of a drug in the absence of support from the sponsor, the responses were assorted. Most of the respondents said that it would be appropriate for a regulatory authority to force a switch against the willingness of a manufacturer if such a move meets public health needs. However, respondents also stated that the most productive and efficient approach to switches would be a collaborative one between the manufacturer and the regulatory authority. The reasons provided to justify a unilateral switch by the regulatory authority were; (a) public health benefit must be the paramount criterion for driving such actions (b) in some therapeutic areas the safest treatment options are available by prescription only and not OTC, and (c) sponsors should not be allowed to wait until the economically opportune time for them to initiate switch proposals.

Some participants said that while they agree with unilateral switching by the regulatory authority in principle, they envisioned legal and intellectual property problems, if the US FDA takes such an action. The legal and intellectual property

difficulties were also the rationale on which the CHPA and PhRMA vigorously opposed the authority of FDA to unilaterally switch drugs to OTC status. Dr. Woodcock, Director, Center for Drug Evaluation & Research (CDER), FDA stated that FDA has the legal authority to unilaterally switch drugs to OTC status during a recent Congressional hearing on this subject. Kaiser Permanente, the largest nonprofit health maintenance organization in America took the position that OTC status must be determined only on the basis of the pharmacological profile of the drug and safe use by consumers irrespective of manufacturers willingness to switch. Well Point Health Networks, a managed care company also agreed with the Kaiser's position and suggested that FDA must take an activist role to reclassify prescription drugs deemed safe for OTC use regardless of sponsor's willingness.

Criteria for OTC classification

A substantial majority of the participants opined that the current OTCness criterion of safety/efficacy of drug, self-treatment of condition and overall public health benefit of a medicinal product in the absence of a learned intermediary as adequate for making decisions on OTC suitability. However, a reasonable portion of the respondents also stated there were inconsistencies in the implementation of these criterion in the decision making process and evaluating OTC suitability. One participant stated that there should not be any limitations on who can petition for reclassification to OTC status in the US. Also, some respondents requested clarifications in the regulatory process for OTC evaluation of prescription medicines.

CHPA, PhRMA, Kaiser Permanente and Well Point Health Networks agreed that the existing regulatory criteria applicable in the estimation of risk-to-benefit ratio

for OTC availability were adequate. The APhA recommended that the FDA must additionally consider the environments surrounding the use of the drug and the disease or symptom for which it is used. Dr. Wolfe suggested that ease of self-diagnosis, self-limited or chronic condition, benefit-to-risk ratio and its evaluation, low potential for abuse, adverse reactions and drug interactions, and long-term prescription use data as six principles that must be used to evaluate potential Rx-to-OTC switch candidates.

A significant theme that was repeatedly observed among the participants was serious concern over the unscientific approval process for non-traditional OTC medicines under the Dietary Supplement Health and Enhancement Act (DSHEA). Almost all respondents felt that the robust scientific and data-driven decision making process followed for most pharmaceutical OTC products as per the OTC Drug Review was completely eliminated for DSHEA products and such was medically unjustifiable.

Suitability of disease conditions for self-medication and drugs for OTC status

The opinion of participants interviewed on the suitability of disease conditions and drug classes for OTC use was diverse. Almost all the participants strongly opposed the OTC use of medicines such as diuretics, antihypertensives, cholesterol-lowering drugs, oral antidiabetic drugs, osteoporosis treatments, antimicrobials and oral contraceptives. But, a reasonable subsection of the participants said that they would be more amenable to OTC status for some of these drug classes (such as cholesterol-lowering drugs, some types of osteoporosis treatments, diuretics and antihypertensives) if pharmacist intervention and prescription are made mandatory in the purchasing process. The Preventive Cardiovascular Nurses Association strongly recommended that FDA consider OTC status for some cholesterol lowering statin medications. Dr. Wolfe

strongly opposed consideration of OTC status for statins. None of the participants thought that antimicrobials should be made OTC and very few groups supported OTC status for oral contraceptives. The National Women's Health Network and the American Life League opposed OTC status for oral contraceptives. But, the National Women's Health Network joined the American Society for Emergency Contraception in strongly supporting OTC status for emergency contraceptives.

The views of respondents were similar on the suitability of conditions such as chronic illnesses (such as asthma), diseases that require an initial diagnosis by a physician (such as a hypercholesterolemia) and hypertension for self-treatment. Respondents were more favorable to certain classes of asthma medications being OTC, if pharmacist involvement were mandatory. Mr. Hutt stated that at the time of the OTC Drug Review, the committees were asked to approach the evaluation of OTC suitability with a very open mind, with no conditions or classes presumed to be unsuitable as the philosophy was to have all drugs available for consideration and deliberation before the committees. The CHPA also advocated a similar approach of open-mindedness without presuming unsuitability and arriving at decisions based on a data-driven and case-specific basis.

The AMA was concerned at a number of prescription drugs used to treat various chronic diseases being considered for switch to OTC status. The AMA recommended that the FDA move with extreme caution in this area. AMA argued that the benefits of physician diagnosis (including other pre-existing conditions), prescription of the right drug at the right dosage, counseling, and monitoring for compliance, therapeutic response and adverse effects for these chronic diseases are very important. In the

AMA's view, to potentially lose the benefit of physician supervision by switching drug products to OTC status would be detrimental to the public health.

Overall, the participants felt that complete elimination of a learned intermediary (physician or pharmacist) would be imprudent and supported a collaborative system where a close relationship between the physician and the pharmacist is preserved with the responsibility for maintenance and monitoring of the treatment placed largely on the pharmacist.

Consumer understanding and behavior

A reasonable proportion of the study participants believed that consumers could neither make a rational selection of treatment regimens nor choose the best way to cure their illness, when there are coexisting prescription and OTC therapies for a certain disease. Further, they also thought that prevention claims for OTC medicines might encourage ill-advised behavior among consumers. Respondents reasoned that consumers are neither trained nor qualified to make such decisions and most often do not have the appropriate information to use medicines properly in an OTC environment.

CHPA asserted that its research showed that 95% of consumers read the labels before using OTC medicines and that there is a very high level of label comprehension. Also, they stated that OTC does not necessarily eliminate the physician from the self-treatment process. National Consumer's League's behavioral research data showed that consumers were willing to learn and had good understanding in some areas of OTC use, but in other aspects they needed professional counseling. APhA and NCPA stated support for methods that assess consumer understanding of proposed labeling that involves the pharmacy and the pharmacist. Dr. Bradford, a researcher in the area of

OTC clinical trials, suggested active surveillance as a tool to estimate how consumers interface with the labeling and use the OTC medicine. One respondent representing a women's health group stated that FDA must ensure that consumers receive unbiased information and not rely solely on manufacturer's advertisements. Mr. Hutt who oversaw the OTC Drug review commented that the review was conducted on the premise that consumers are intelligent, can be educated, interested in their own health and want a share of their healthcare decisions.

Approval of new OTC medicines

When asked if the first drug to enter the OTC market should be the "best" drug in terms of benefit-to-risk ratio within a therapeutic class, a majority of respondents concurred. A majority of the respondents agreed that the availability of a "better" OTC product in terms of efficacy or safety should not affect the status of products already in the OTC market for treatment of the same condition within a therapeutic class. Additionally, participants stated that when newer nonprescription products become available within a therapeutic class, older therapies that may provide less benefit or more risk should not be removed from the market or their labeling should not be revised. On the issue of direct-to-OTC marketing (a new chemical entity directly marketed as an OTC product without being a prescription medicine for some duration), there was universal agreement that products must be marketed as a prescription medicine under the supervision of a learned intermediary for some duration before reclassification to OTC status may be considered. Respondents stated that a drug's safety profile cannot be understood based solely on controlled clinical trials during

development and surveillance during real-world clinical practice is necessary before OTC status may be considered.

Discussion

As with any study, this study is subject to limitations and the results must only be interpreted within the context of any such limitations. An important limitation of this study is that the study sample population may not accurately represent the overall population of stakeholders. Although attempts were made to interview all stakeholders, it is rarely feasible to fully realize this objective. Also, responses are influenced by the inherent biases of the respondents and must be accounted in analyzing the data. Despite the limitations, these results are useful to discern the attitudes of important stakeholders on regulation of nonprescription medicines. This assertion is reinforced, as the study is exploratory in nature and was not designed to test any specific hypotheses. Moreover, the absence of any information in the global context related to these important issues accentuates the significance of these results.

Study results demonstrate that opinions of respondents over most issues were wide-ranging in nature. This observation is reasonable as all stakeholders do not share the same interests and their positions are correspondingly influenced. It is evident from the results that stakeholders' positions are developed to be favorable to their underlying interests. However, optimal regulatory policy must be formulated to maximize the public health benefit. Thus, unhindered access to potent drug products and their safe use by consumers must be cautiously balanced to achieve effective self-medication.

Results suggest that proposals to improve US regulatory structure for OTC medicines may include finalizing the pending OTC monographs and increasing

pharmacist intervention and/or prescriptive authority for OTC medicines. The latter proposal has been a controversial one for sometime and as discussed earlier has been vigorously opposed by the CHPA and the AMA. However, views from respondents in countries that have a pharmacist class of OTC medicines show that such a class can be enormously beneficial in ensuring safe and effective use of OTC drug products. Results from the earlier part of this study also evidenced very strong support for a pharmacist class of OTC medicines. Additionally, as the OTC arena in the US evolves and more potent prescription drug products are considered for OTC status, the pharmacist intervention can be employed as an effective tool in increasing the public health benefit and decreasing the public health risk.

Evidence shows support for regulatory agencies to be able to unilaterally switch drug products and that such decisions must be based only on the overall public health benefit considerations. Study observations indicate that regulatory agencies must pursue a collaborative approach with manufacturers in switching drug products to OTC status. Based on the Australian system, it may be helpful to include “judicious use of medicines” to the current OTCness criterion as applied by the FDA in evaluating drug products for OTC status. Judicious use is defined as “the use of medicines only when appropriate with non-medicinal alternatives considered as needed” as per the Australian system. The urgency to correct the current non data-driven regulatory process for marketing of dietary supplements as per DSHEA is strongly supported by the study results. The importance of addressing safety of products marketed through DSHEA process cannot be overemphasized, as dietary supplements are rapidly becoming a substantial part of the OTC armamentarium.

Observations suggest that the suitability of disease conditions for self-treatment and drugs for OTC use must be evaluated without any presumption or bias in a case specific manner based on a data-driven approach with overall public health benefit as the paramount objective. Respondents stated that consumers are inherently intelligent and if educated adequately can make the decisions resulting in the responsible use of OTC medicines. In this regard, the onus of consumer education must be shared between the manufacturer and the regulatory authority to ensure that consumers have complete and truthful information that will enable them to use OTC medicines safely and effectively. Again, the utility of a pharmacist as a learned intermediary is invaluable in this regard and efforts to bridge the gap between the physician and the pharmacist to enhance the quality of healthcare delivery must be seriously considered. Results also suggest that marketing status of medicines should not be affected by the availability of newer or better medicines as it would be desirable to have a variety of treatment options as individuals do not respond to pharmacological agents in a uniform manner.

Conclusions

This study explored the opinions of thirty six key opinion leaders and stakeholders in the area of OTC medicines regulation from the United States, United Kingdom, Australia and Canada on issues such as the OTC regulatory environment, role of regulatory agency in Rx-to-OTC switches, criteria for OTC classification, suitability of drugs for OTC status and disease conditions for self-medication, consumer behavior and understanding of OTC medicines and the approval of new OTC medicines. Results suggest that potential improvements to the US regulatory framework can include creation of an intermediate, pharmacist-controlled class of OTC medicines, delineation

of data requirements in a guidance document to support a switch petition, regulation of nontraditional medicines (dietary supplements and nutraceuticals) also as per current OTC standards of pre-market demonstration of safety and efficacy, and, the development of global OTC monographs.

Responses showed support for regulatory agencies to unilaterally switch drug products and such decisions to be based only on the overall public health benefit considerations. A substantial majority of all respondents believed that consumers are inherently intelligent and if educated adequately can make the decisions resulting in the responsible use of OTC medicines.

References

1. Over-the-Counter Drug Products; Public Hearing, *Federal Register*, 65, 24704-24706 (2000).

Appendix

List of statements in the interview questionnaire

1. Current regulatory environment for marketing nonprescription medicines (NPM) in your country is adequate.
2. Your country can learn from different nonprescription medicine regulatory environments and marketing systems within other developed nations.
3. US should adopt a regulatory framework that includes an intermediate, pharmacist-controlled class of nonprescription medicines (i.e. behind-the-counter medicines).
(US ONLY)

4. The relevant regulatory Agency in your country should actively propose nonprescription marketing of a prescription drug in the absence of support from the drug manufacturer (sponsor).
5. The relevant regulatory Agency in your country should be more active in unilaterally initiating switches of prescription medicines to nonprescription use.
6. Current criteria used by the relevant regulatory Agency in your country in rendering decisions on availability of nonprescription drug products is adequate.
7. The following types of diseases/illnesses are suitable for treatment with nonprescription drug products:
 - a. Chronic illnesses (such as asthma)
 - b. Diseases that require initial diagnosis by a physician (such as hypercholesterolemia, i.e. high cholesterol)
 - c. Diseases (such as hypertension) that, if left untreated or are inadequately treated can lead to serious morbidity or mortality
8. The following are specific classes of medicines that are not currently marketed as nonprescription medicines that should be available without a prescription:
 - a. Diuretics
 - b. Antihypertensive drugs
 - c. Cholesterol lowering drugs
 - d. Oral antidiabetic drugs
 - e. Treatments for osteoporosis (including its prevention)

f. Antimicrobials

g. Oral contraceptives

9. Rational selection of treatment regimens by consumers may be ensured when there are coexisting prescription and nonprescription therapies for a certain disease.
10. Patients know the best ways to treat their illnesses in an environment with coexisting prescription and nonprescription therapies for a certain disease.
11. The risks and benefits to individuals and public health should be assessed and weighed in any decision on nonprescription marketing of drug products (for example, the potential benefits of nonprescription antimicrobial agents with the potential risks to society at large of the development of resistant organisms).
12. Prevention claims for nonprescription medicines encourage ill-advised behavior (for example, use of an nonprescription cholesterol lowering drug would allow patients to ignore other needed interventions such as smoking cessation, dietary discretion and management of other risk factors).
13. Within a therapeutic class, the first drug to enter the nonprescription market should be the “best” drug in terms of the benefit-to-risk ratio.
14. Within a therapeutic class, the availability of a “better” nonprescription product in terms of efficacy or safety should affect the status of products already on the nonprescription market for treatment of the same condition.
15. When newer nonprescription products become available within a therapeutic class, older therapies that may provide less benefit or more risk should be either removed from the market or their labeling should be revised.

16. Initiatives to market at least some nontraditional medicines (dietary supplements, vitamins, nutraceuticals and other traditional medicines) as regular OTC drug products by subjecting them to the same rigorous premarketing scientific evaluation and clinical review criteria should be promoted. (US ONLY)
17. Direct-to-consumer marketing of prescription drug products adversely influences reclassification to OTC status and availability of new OTC drug products. (US ONLY)
18. Initiatives to develop and establish globally acceptable monographs for nonprescription drug products, at least, within the developed world should be promoted.
19. The US FDA should issue a "Guidance for Industry" document on the reclassification of prescription products to OTC status describing the nature of evidence required to substantiate such applications. (US ONLY)
20. Assuming a new chemical entity meets all regulatory requirements necessary for nonprescription classification, it should still be marketed as prescription medicine for a specified duration before reclassification to nonprescription status may be considered.

Table 1: Description of participants interviewed for this study

Participant	Description
Australia	
Participant #1	Community pharmacist affiliated with the group of independent retail pharmacists
Participant #2	Community pharmacist and Self-care specialist affiliated with the group of practicing pharmacists
United Kingdom	
Participant #3	Community pharmacist, lawyer and professor affiliated with the University of Nottingham
Participant #4	Health care economist and professor affiliated with the University of London
Participant #5	Regulatory specialist affiliated with the industry group of manufacturers of nonprescription medicines
Canada	
Participant #6	Regulatory specialist affiliated with the industry group of manufacturers of nonprescription medicines
Participant #7	Community pharmacist affiliated with the group of practicing pharmacists
Participant #8	Pharmacy regulatory professional affiliated with the group of pharmaceutical regulatory authorities
Participant #9	Professor and researcher in OTC medicines affiliated with University of Saskatchewan
United States of America	
Participant #10	Physician, professor and researcher in OTC medicines affiliated with Northwestern University
Participant #11	Community pharmacist and lawyer affiliated with the group of practicing pharmacists
Participant #12	Community pharmacist, clinical researcher and professor affiliated with Drake University
Participant #13	Physician, professor and expert advisor to US FDA on OTC medicines affiliated with University of Pennsylvania

Table 1: Description of participants interviewed for this study

Participant	Description
Participant #14	Community pharmacist, self-care researcher and professor affiliated with University of Florida
Participant #15	Pharmacist, Ex-FDA and Ex-Industry leader affiliated with a food and drug law think tank
Participant #16	Community pharmacist, self-care researcher, author and professor affiliated with Southwest Oklahoma State University
Participant #17	Representative of a women's health consumer activist group
Participant #18	Pharmacoeconomic policy expert, researcher and professor affiliated with the University of Minnesota

Table 2: Description of participants whose written statements were used for this study

Participant	Description/Affiliation	Country
Dr. Michael Maves, Dr. Bill Soller and Ms. Eve Bachrach	Consumer Health Products Association	USA
Mr. Doug Hoey	National Community Pharmacist's Association	USA
Dr. Ratcliffe Anderson Jr.	American Medical Association	USA
Dr. Sidney Wolfe	Physician and consumer activist affiliated with Public Citizen	USA
Mr. Anthony Baruetta	Lawyer and executive with Kaiser Permanente	USA
Ms. Linda Golodner	National Consumer's League	USA
Mr. Steve Francesco	Head of Rx-to-OTC Switch Consulting firm Francesco International	USA
Mr. Peter Barton Hutt	Food & Drug lawyer and Ex-FDA staff member associated with the OTC Drug Review process	USA
Mr. Russell Bantham	Pharmaceutical Research and Manufacturers Association (PhRMA)	USA
Ms. Judie Brown	American Life League	USA
Ms. Tara Shochet	American Society for Emergency Contraception	USA
Ms. Suzanne Hughes	Registered Nurse and President Lipid Nurse Task Force	USA
Mr. Robert Seidman	Chief Pharmacy Officer, Wellpoint Health Network	USA
Dr. Randy Juhl	Ex-FDA Advisory Committee chairman, Pharmacist, CHPA associate and Dean, University of Pittsburgh, School of Pharmacy	USA
Dr. David Bradford	Clinical researcher specializing in Rx-to-OTC switches with Pegus Research	USA
Mr. Robert G Pinco	Food & Drug lawyer and Ex-FDA staff member associated with the OTC Drug Review process	USA
Mr. David Steinberg	Food & Drug lawyer	USA
	British Medical Association	United Kingdom

SECTION III

APPENDIX A

LIST OF PUBLICATIONS

The following is a list of the journals in which manuscripts from this dissertation have been or will be published:

1. Achanta A.S., Willey-Temkin C., and Rhodes C.T., "Attitudes and Opinions Towards Regulatory Aspects of Nonprescription Medicines", accepted for publication in *Regulatory Affairs Journal*. (Manuscript VII)
2. Achanta A.S. and Rhodes C.T., "Examination of Proposed OTC status for Nonsedating Antihistamines", *Clinical Research & Regulatory Affairs*, 19(1): 1-12 (2002). (Manuscript VI)
3. Achanta A.S. and Rhodes C.T., "Evaluation of Proposed OTC Switch for Lovastatin", *Clinical Research & Regulatory Affairs*, 18(1&2): 83-104 (2001). (Manuscript V)
4. Achanta A.S. and Rhodes C.T., "The Metaproterenol OTC Switch in the USA", *Regulatory Affairs Journal*, 12(8): 641-644 (2001). (Manuscript IV)

APPENDIX B

Appendix B collates a variety of supporting information that would aid clearer understanding of the methodological details, discussion and inferences presented in the earlier manuscripts. The data included here are the appropriate transcripts, briefing material used at the FDA advisory committee meetings discussed in this dissertation, electronic files pertaining to the electronic survey administered and the database of the results collected from the survey. Due to the voluminous and digital nature of this supporting data, the information is presented in electronic format on a compact disk. The compact disk is attached to the dissertation.

APPENDIX C

This appendix presents a brief chronological list of some key milestones in the history of food and drug regulation in the United States that are relevant to this dissertation. This information is presented to help the reader provide a historical perspective on developments related to drug regulation and obtain a detailed understanding of some discussions presented in the dissertation. The list provided below is an abridged version of "Milestones in U.S. Food and Drug Law History" published by the US FDA. The complete list may be accessed at <http://www.fda.gov/opacom/backgrounders/miles.html>

1820

Eleven physicians meet in Washington, D.C., to establish the U.S. PHARMACOPEIA, the first compendium of standard drugs for the United States.

1862

PRESIDENT LINCOLN appoints a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This was the beginning of the Bureau of Chemistry, the predecessor of the Food and Drug Administration.

1880

PETER COLLIER, chief chemist, U.S. Department of Agriculture, recommends passage of a national food and drug law, following his own food adulteration investigations. The bill was defeated, but during the next 25 years more than 100 food and drug bills were introduced in Congress.

1883

DR. HARVEY W. WILEY becomes chief chemist, expanding the Bureau of Chemistry's food adulteration studies. Campaigning for a federal law, Dr. Wiley is called the "Crusading Chemist" and "Father of the Pure Food and Drugs Act".

1898

Association of Official Agricultural Chemists (now AOAC International) establishes a COMMITTEE ON FOOD STANDARDS headed by Dr. Wiley. States begin incorporating these standards into their food statutes.

1902

The BIOLOGICS CONTROL ACT is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.

Congress appropriates \$5,000 to the Bureau of Chemistry to study CHEMICAL PRESERVATIVES AND COLORS and their effects on digestion and health. Dr. Wiley's studies draw widespread attention to the problem of food adulteration. Public support for passage of a federal food and drug law grows.

1906

The original FOOD AND DRUGS ACT is passed by Congress on June 30 and signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks and drugs. The MEAT INSPECTION ACT is passed the same day. Shocking disclosures of unsanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines were the major problems leading to the enactment of these laws.

1911

In U.S. v. JOHNSON, the Supreme Court rules that the 1906 Food and Drugs Act does not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug.

1912

Congress enacts the SHERLEY AMENDMENT to overcome the ruling in U.S. v. Johnson. It prohibits labeling medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove.

1913

GOULD AMENDMENT requires that food package contents be "plainly and conspicuously marked on the outside of the package in terms of weight, measure, or numerical count."

1927

The Bureau of Chemistry is reorganized into two separate entities. Regulatory functions are located in the FOOD, DRUG, AND INSECTICIDE ADMINISTRATION, and nonregulatory research is located in the BUREAU OF CHEMISTRY AND SOILS.

1930

The name of the Food, Drug, and Insecticide Administration is shortened to FOOD AND DRUG ADMINISTRATION (FDA) under an agricultural appropriations act.

1933

FDA recommends a complete revision of the obsolete 1906 FOOD AND DRUGS ACT. The first bill is introduced into the Senate, launching a five-year legislative battle.

1937

ELIXIR OF SULFANILAMIDE, containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom are children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.

1938

THE FEDERAL FOOD, DRUG, AND COSMETIC (FDC) ACT of 1938 is passed by Congress, containing new provisions:

- Extending control to cosmetics and therapeutic devices.
- Requiring new drugs to be shown safe before marketing-starting a new system of drug regulation.
- Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases.
- Providing that safe tolerances be set for unavoidable poisonous substances.
- Authorizing standards of identity, quality, and fill-of-container for foods.
- Authorizing factory inspections.
- Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.

Under the WHEELER-LEA ACT, the Federal Trade Commission is charged with overseeing advertising associated with products otherwise regulated by FDA, with the exception of prescription drugs.

1940

FDA TRANSFERRED from the Department of Agriculture to the Federal Security Agency, with Walter G. Campbell appointed as the first Commissioner of Food and Drugs.

1941

INSULIN AMENDMENT requires FDA to test and certify purity and potency of this life-saving drug for diabetes.

1943

In U.S. v. DOTTERWEICH, the Supreme Court rules that the responsible officials of a corporation, as well as the corporation itself, may be prosecuted for violations. It need not be proven that the officials intended, or even knew of, the violations.

1944

PUBLIC HEALTH SERVICE ACT is passed, covering a broad spectrum of health concerns, including regulation of biological products and control of communicable diseases.

1945

PENICILLIN AMENDMENT requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments extended this requirement to all antibiotics. In 1983 such control was found no longer needed and was abolished.

1949

FDA publishes GUIDANCE TO INDUSTRY for the first time. This guidance, "Procedures for the Appraisal of the Toxicity of Chemicals in Food," came to be known as the "black book."

1950

In ALBERTY FOOD PRODUCTS CO. v. U.S. , a court of appeals rules that the directions for use on a drug label must include the purpose for which the drug is

offered. Therefore, a worthless remedy cannot escape the law by not stating the condition it is supposed to treat.

1951

DURHAM-HUMPHREY AMENDMENT defines the kinds of drugs that cannot be safely used without medical supervision and restricts their sale to prescription by a licensed practitioner.

1952

In U.S. v. CARDIFF, the Supreme Court rules that the factory inspection provision of the 1938 FDC Act is too vague to be enforced as criminal law.

FDA CONSUMER CONSULTANTS are appointed in each field district to maintain communications with consumers and ensure that FDA considers their needs and problems.

1953

FEDERAL SECURITY AGENCY becomes the Department of Health, Education, and Welfare (HEW).

FACTORY INSPECTION AMENDMENT clarifies previous law and requires FDA to give manufacturers written reports of conditions observed during inspections and analyses of factory samples.

1955

HEW SECRETARY OVETA CULP HOBBY appoints a committee of 14 citizens to study the adequacy of FDA's facilities and programs. The committee recommends a substantial expansion of FDA staff and facilities, a new headquarters building, and more use of educational and informational programs.

The DIVISION OF BIOLOGICS CONTROL became an independent entity within the National Institutes of Health, after polio vaccine thought to have been inactivated is associated with about 260 cases of polio.

1958

FDA publishes in the Federal Register the first list of SUBSTANCES GENERALLY RECOGNIZED AS SAFE (GRAS). The list contains nearly 200 substances.

1962

THALIDOMIDE, a new sleeping pill, is found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation.

KEFAUVER-HARRIS DRUG AMENDMENTS passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.

1965

DRUG ABUSE CONTROL AMENDMENTS are enacted to deal with problems caused by abuse of depressants, stimulants and hallucinogens.

1966

FDA contracts with the National Academy of Sciences/National Research Council to evaluate the EFFECTIVENESS OF 4,000 DRUGS approved on the basis of safety alone between 1938 and 1962.

FAIR PACKAGING AND LABELING ACT requires all consumer products in interstate commerce to be honestly and informatively labeled, with FDA enforcing provisions on foods, drugs, cosmetics, and medical devices.

1968

FDA forms the DRUG EFFICACY STUDY IMPLEMENTATION (DESI) to implement recommendations of the National Academy of Sciences investigation of effectiveness of drugs first marketed between 1938 and 1962.

1970

In *UPJOHN v. FINCH* the Court of Appeals upholds enforcement of the 1962 drug effectiveness amendments by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy.

FDA requires the first PATIENT PACKAGE INSERT: oral contraceptives must contain information for the patient about specific risks and benefits.

The COMPREHENSIVE DRUG ABUSE PREVENTION AND CONTROL ACT replaces previous laws and categorizes drugs based on abuse and addiction potential compared to their therapeutic value.

1972

OVER-THE-COUNTER DRUG REVIEW begun to enhance the safety, effectiveness and appropriate labeling of drugs sold without prescription.

REGULATION OF BIOLOGICS-including serums, vaccines, and blood products-is transferred from NIH to FDA.

1973

THE U.S. SUPREME COURT upholds the 1962 drug effectiveness law and endorses FDA action to control entire classes of products by regulations rather than to rely only on time-consuming litigation.

CONSUMER PRODUCT SAFETY COMMISSION created by Congress; takes over programs pioneered by FDA under 1927 Caustic Poison Act, 1960 Federal Hazardous Substances Labeling Act, 1966 Child Protection Act, and PHS accident prevention activities for safety of toys, home appliances, etc.

1976

VITAMINS AND MINERALS AMENDMENTS ("Proxmire Amendments") stop FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

1982

TAMPER-RESISTANT PACKAGING REGULATIONS issued by FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules. The Federal Anti-Tampering Act passed in 1983 makes it a crime to tamper with packaged consumer products.

FDA publishes first RED BOOK (successor to 1949 "black book"), officially known as Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food.

1983

ORPHAN DRUG ACT passed, enabling FDA to promote research and marketing of drugs needed for treating rare diseases.

1984

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective. At the same time, the brand-name companies can apply for up to five years additional patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process.

1985

AIDS TEST FOR BLOOD approved by FDA in its first major action to protect patients from infected donors.

1987

INVESTIGATIONAL DRUG REGULATIONS REVISED to expand access to experimental drugs for patients with serious diseases with no alternative therapies.

1988

FOOD AND DRUG ADMINISTRATION ACT of 1988 officially establishes FDA as an Agency of the Department of Health and Human Services with a Commissioner of Food and Drugs appointed by the President with the advice and consent of the Senate, and broadly spells out the responsibilities of the Secretary and the Commissioner for research, enforcement, education, and information.

1991

Regulations published to ACCELERATE THE REVIEW OF DRUGS for life-threatening diseases.

1992

GENERIC DRUG ENFORCEMENT ACT imposes debarment and other penalties for illegal acts involving abbreviated drug applications.

PRESCRIPTION DRUG USER FEE ACT requires drug and biologics manufacturers to pay fees for product applications and supplements, and other services. The act also requires FDA to use these funds to hire more reviewers to assess applications.

1994

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT establishes specific labeling requirements, provides a regulatory framework, and authorizes FDA to promulgate good manufacturing practice regulations for dietary supplements. This act defines "dietary supplements" and "dietary ingredients" and classifies them as food. The act also establishes a commission to recommend how to regulate claims.

FDA announces it could consider REGULATING NICOTINE in cigarettes as a drug, in response to a Citizen's Petition by the Coalition on Smoking or Health.

1995

FDA declares CIGARETTES to be "drug delivery devices." Restrictions are proposed on marketing and sales to reduce smoking by young people.

1997

FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in Agency practices since 1938. Provisions include measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods.

SUMMARY OF CONCLUSIONS

Synopsis

The use of over-the-counter (OTC) medicines and interest in self-care is rapidly increasing worldwide. This dissertation presents the first and, perhaps, the most comprehensive analysis of the classification of nonprescription medicines and Rx-to-OTC switch criteria in the United States, United Kingdom, Canada, Japan and Australia. The US FDA's overall switch regulatory policies were investigated through the application of case-history evaluations. An innovative investigational method that utilized a combination of web-based global electronic survey instrument and a telephone interview survey instrument has been applied to measure and study the attitudes and opinions of important stakeholders on global issues of vital interest to regulation of nonprescription medicines. The data collected has been used to provide answers to some questions posed by the US FDA as part of its overall review of regulation of OTC products in the US.

This study demonstrates the utility of electronic communication in the rapid and effective completion of a global survey. Also, the electronic survey instrument is presented as an efficient alternative to traditional questionnaire-by-mail survey technique. Data shows that the OTC regulatory model in the United States may be improved. Evidence indicates that principles upon which approaches for improvements must be based are: an objective evaluation of pharmacist class of OTC medicines, development of effective consumer education tools, increase in regulation of non-traditional OTC medicines, not all disease conditions and drug classes are suitable for self-treatment, a collaborative approach by FDA towards switching that includes all

stakeholders is more favored, decisions on switch petitions must be case-specific without a presumptive bias and public health benefit must be the paramount evaluation criterion.

The significance of information presented in this dissertation is amplified as this area has received little academic attention and information is not readily available. It is proposed that an examination of the interactive effects between scientific, regulatory and economic principles affecting nonprescription medicines and their optimization to maximize public health benefit would be appropriate for subsequent research.

List of conclusions

Presented below in detail are some of the significant and original findings resulting from this study:

1. Globally, healthcare systems are changing significantly to affect the use and attitudes toward over-the-counter (OTC) medicines and interest in self-care is rapidly increasing. In recent years, self-medication has undergone a dramatic change due to the advent of herbal medicines, dietary supplements, nutraceuticals and health foods in addition to traditional nonprescription medicines, and, increasing societal preferences towards greater individual control over the use of medicines. It is widely believed that responsible use of OTC medicines can lead to overall cost savings and public health benefit. Hence, the regulatory framework related to nonprescription medicines has become an important priority for regulatory authorities, academicians and the industry.
2. This dissertation presents the first and, perhaps, the most comprehensive analysis of the classification of nonprescription medicines and Rx-to-OTC switch criteria in the

United States, United Kingdom, Canada, Japan and Australia. A new approach to investigating US FDA's overall switch regulatory policies through the application of case-history evaluations has been utilized. The significance of information elicited through this dissertation is amplified as this area has received little academic attention and only sparse data is available.

3. A comparative examination of the OTC regulatory structures in the United States, United Kingdom, Canada and Australia shows universal recognition of OTC medicines as vital for public health care and remarkable differences in the classification of OTC medicines and criterion used for evaluation of Rx-to-OTC switch applications. A substantial majority of all survey respondents endorsed the development of globally acceptable monographs for OTC drug products within the developed world, so that scientific knowledge and best practices may be shared leading to efficiencies in regulation of nonprescription medicines and positive public health outcomes.
4. An overwhelming majority of survey respondents stated that the paramount criterion for deciding OTC status must be overall public health benefit. Examination of FDA's application of switch regulatory policy in the case of nicotine replacement therapy, wherein nicotine, a recognized addictive drug, was made available without a prescription as a smoking cessation aid, demonstrates that FDA's action was in line with the survey finding. Post switch evidence showed that OTC reclassification of Nicorette[®] achieved the anticipated goal of balancing increased access with decreased control and led to public health benefit. This switch case also emphasizes the need to expand the use of innovative consumer education, communication tools

and behavioral support programs successfully pioneered and demonstrated by the sponsor.

5. The case of metaproterenol OTC switch by the FDA upon its own initiative offers valuable information in the comprehension of FDA's application of OTC switch regulatory policy. The FDA is encouraged to initiate switch proposals that it considers to be safe and effective in an OTC environment and offer overall public health benefit. The learning from the failed metaproterenol switch emphasizes that a collaborative effort with the sponsor and all interested parties is more likely to result in a scientifically robust switch decision. Hence, the Agency must properly manage the consideration of switch proposals that it has initiated by ensuring active participation of all possible stakeholders that may be impacted by its rulemaking.
6. It is possible to reason that for drugs such as lovastatin, used for chronic and asymptomatic conditions, where FDA maintains that the involvement of a learned intermediary is necessary, it may be feasible to favorably balance the benefit to risk by classifying them under an intermediate, pharmacist controlled class of drugs, where a physician's prescription is not required, but pharmacists may dispense medication based upon patient consultation and their professional judgment.
7. An overwhelming majority (80%) of American respondents surveyed believed that the US should adopt a regulatory framework that includes an intermediate, pharmacist-controlled class of nonprescription medicines. Also, respondents from outside the United States endorsed the utility of a pharmacist-controlled class of nonprescription medicines. The physician and industry interest groups vigorously opposed such a class. Evidence collected strongly supports the consideration and

evaluation of a pharmacist-controlled class of nonprescription medicines in the United States. Efforts to bridge the gap between physicians, pharmacists and patients to enhance the quality of healthcare delivery must be seriously considered.

8. An innovative investigational method that utilized a combination of web-based global electronic survey instrument and a telephone interview survey instrument has been applied to measure and study the attitudes and opinions of important stakeholders on global issues of vital interest to regulation of nonprescription medicines. This study demonstrates the utility of electronic communication in the rapid and effective completion of a global survey. Also, the electronic survey instrument is presented as an efficient alternative to traditional questionnaire-by-mail survey technique. A total of 473 responses were received from United States, Australia, United Kingdom and Canada through the electronic survey instrument. Additionally, the opinions of thirty-six stakeholders (to include interest groups and key opinion leaders) in great detail from United States, Australia, United Kingdom and Canada were collected and examined.
9. Some significant inferences based on the evidence presented in this dissertation on OTC issues of global interest and, in particular to the FDA, are:
 - a. A majority of American respondents believed that the current regulatory environment for marketing OTC medicines in the US was inadequate
 - b. Two thirds of the respondents believed that the US FDA could learn from different OTC regulatory environments and marketing systems within developed nations.

- c. More than 8 in 10 Americans opined that US FDA should issue a "guidance for industry" document on the reclassification of prescription products to OTC status describing the nature of the evidence required to substantiate such applications.
- d. On the issue of a regulatory agency actively proposing OTC marketing of a drug in the absence of support from the sponsor, the response was varied. American opinion was evenly split with 40% disagreeing, 39% agreeing and 21% being undecided. On the related question of a regulatory agency unilaterally initiating switches of prescription medicines to OTC use, American opinion was unclear with 43% agreeing, 42% disagreeing and 15% being undecided. Roughly 70% of Australians disagreed and 52% of Britains agreed with this idea. A majority of Canadians (45%) rejected this notion. Again, the industry interest groups vigorously opposed this proposal. This observation is most pertinent in the current context of proposed OTC status for second-generation antihistamines. Also, if the FDA unilaterally switches the three antihistamines to OTC status, it will be setting a precedent and the procedural details of such an action are unknown. However, there was universal agreement that a collaborative switch process between the FDA and all stakeholders is most favored.
- e. The ambivalence of Americans on the adequacy of US FDA reclassification criteria reinforces the dissatisfaction of Americans with their OTC regulatory framework.

- f. The respondents almost unanimously stated that the risks and benefits to individuals and public health should be assessed and weighed in any decision on OTC marketing of drug products. 9 in 10 Americans stated that initiatives to market at least some nontraditional medicines (dietary supplements and nutraceuticals) as regular OTC products by subjecting them to the same rigorous premarketing scientific evaluation and clinical review criteria should be promoted. Most respondents added that this is perhaps the most important public health issue that FDA should address in the area of OTC medicines regulation.
- g. Conditions like asthma, hypertension and medications like diuretics, antihypertensives, oral antidiabetics and antinfectives are unsuitable for self-treatment. The opinions over hypercholesterolemia and osteoporosis are complex and divided. Whereas complete lack of healthcare professional intervention does not have any support, support exists for nonprescription use with pharmacist or nurse intervention. Oral contraceptives could also be classified similarly, but some women's health interest groups opposed OTC status.
- h. Consumers may not always possess the knowledge and commitment to responsibly use OTC medicines without being assisted by a learned intermediary. It is important for consumers to responsibly use OTC medicines and the burden of effectively educating the general public and managing the consumer behavior lies on the industry, public and professional groups, regulatory authority and consumers themselves.

- i. The approval of new OTC medicines should not in any way affect the status of existing or already available OTC products.
- j. A drug's safety profile cannot be understood based solely on controlled clinical trials during development and surveillance during real-world clinical practice is necessary.

10. At the time of this study, tremendous activity related to scientific and regulatory aspects of nonprescription medicines is underway globally. These aspects of OTC medicines are beginning to receive attention and scientific examination. The body of relevant reports currently available on this subject matter is not substantial. The author believes that this dissertation serves as an early and comprehensive exploration of this subject and contributes to filling the existing vacuum. It is not possible to have addressed all issues in this dissertation, and, numerous challenging questions in this area remain that present opportunities for subsequent research. Some findings, observations and proposals in this dissertation allow for the formulation of specific constructs suitable for further examination. This dissertation did not focus on economic aspects of global nonprescription medicines. An examination of the interactive effects between scientific, regulatory and economic principles affecting nonprescription medicines and their optimization to maximize public health benefit would be intellectually stimulating and invaluable.

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