2012

FACTORS INFLUENCING PHARMACISTS' DECISION TO REPORT ADVERSE EVENTS RELATED TO DIETARY SUPPLEMENTS

Ali M. Alhammad
Virginia Commonwealth University

FACTORS INFLUENCING PHARMACISTS' DECISION TO REPORT ADVERSE EVENTS RELATED TO DIETARY SUPPLEMENTS

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

By

ALI MOHAMAD ALHAMMAD
Bachelor of Pharmacy, King Saud University, Riyadh, Saudi Arabia, 2001
Master of Science, Pharmaceutical Sciences, Virginia Commonwealth University, 2009

Director: Spencer E. Harpe, PharmD, PhD, MPH
Associate Professor, Department of Pharmacotherapy and Outcomes Science

Virginia Commonwealth University
Richmond, Virginia
August 2012

Acknowledgement

I would like to thank my advisor Dr. Spencer E. Harpe for all of his time, advice and endless support throughout this study. Without his assistance, guidance and broad knowledge, this project would not have been possible. Dr. Harpe, I have learned so many things from you under your mentorship during the past five years. I would also like to thank my committee members Dr. Norman Carroll, Dr. Michael A Pyles, Dr. Lisa Phipps and Dr. Jo Lynne Robins. Completion of this project would not happen without your directions and help.

I have especial thanks to my beloved wife Wasilah for all you have put up with and give in the past five years. My daughters Wala and Hawra and my little boy Hassan, thank you for the happiness and joyfulness you surrounded me with. My mom and dad back there in Saudi Arabia, thank you for your prayers and support. Without the love and continuous support of all members of my family throughout these past five years, completing of this project and write up of dissertation would not have been possible.

Table of Contents

Page

List of Tables

Page

List of Figures

Page

List of Abbreviations

Adaptive Conjoint Analysis ..... ACA

Adverse Event Reporting System ..... AERS

Adverse Events ..... AE

Center for Food Safety and Applied Nutrition .....CFSAN

Centers for Disease Control ..... CDC

Complementary and Alternative Medicine ..... CAM

Confidence Interval..... CI`

Conjoint Analysis ..... CA

Current Good Manufacturing Practices .....cGMPs

Department of Health and Environment .....NMDHE

Dietary Supplement ..... DS

Dietary Supplement and Nonprescription Drug Consumer Protection Act .....DSNDCPA

Dietary Supplement Health and Education Act ..... DSHEA

Discrete Choice Analysis ..... DCA

Eosinophil ..... EOS

Eosinophilia-Myalgia Syndrome ..... EMS

Food and Drug Administration .....FDA

Government Accountability Office .....GAO

Morbidity and Mortality Weekly Report ..... MMWR

National Health and Nutrition Examination Survey ..... NHANES

National Health Interview Survey ..... NHIS

National Health Interview Survey ..... NHIS

National Institutes of Health ..... NIH

Natural Health Products.....NHP

New Dietary Ingredient..... NDI

Nonvitamin/Nonmineral ..... NVNM

Office of Dietary Supplements .....ODS

Over The Counter .....OTC

Poison Control Center.....PCC

Randomized Controlled Trial .....RCT

Abstract

FACTORS INFLUENCING PHARMACISTS' DECISION TO REPORT OF ADVERSE EVENTS RELATED TO DIETARY SUPPLEMENTS

By Ali Mohammad Alhammad, BPharm, MS

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2012

Director: Spencer E. Harpe, PharmD, PhD, MPH
Associate Professor, Department of Pharmacotherapy and Outcomes Science

***Background*:** The increasing consumption of dietary supplements (DS) has drawn the attention of regulatory agencies, researchers and healthcare professionals. The US Food and Drug Administration (FDA) does not require premarketing assessment of DS considering them safe unless proven otherwise. However, the reporting rate of DS adverse events (DS-AE) is low.

***Objective*:** To describe pharmacists' attitudes and knowledge of DS and DS information resources, and to determine the importance of selected attributes in pharmacists' decisions to report a DS-AE.

***Methods*:** A convenience sample of practicing pharmacists in Virginia was surveyed using a web-based self-administered questionnaire. A conjoint analysis exercise was developed using several scenarios based on a set of five attributes: patient's age, initiation of DS, last modification in drug therapy, evidence supporting the AE, and outcome of the AE. Participants were asked to indicate their decision to report the AE in each scenario to prescriber, drug manufacturer, DS manufacturer and FDA on a 6-point ordered scale. Participants' attitude, knowledge of DS, demographic information, and DS information resources were also requested. Linear regression models were used to determine the relative importance of the profile attributes on a pharmacist's decision to report the AE. The effects of other characteristics on the importance of the attributes were assessed.

Results: Participants' overall attitudes were relatively positive for the clinical use of DS but negative for safe of DS. Formal training on DS was associated with better knowledge of DS regulation. The average knowledge score of DS identification was relatively good but was low for DS regulation. Lexi-Comp® was the most widely used and available information resource and the Natural Medicines Comprehensive Database was the most useful once. The most important attribute that a pharmacist considered in the decision to report a DS-AE to DS manufacturer, drug manufacturer and FDA was the outcome of the

AE followed by the evidence supporting the AE. Ranking of these two factors was the reversed in reporting to prescriber.

Conclusions: Outcome and evidence of the AE are the most important factors participants considered when reporting. Other characteristics do not have an impact on the relative importance of the attributes.

CHAPTER 1 INTRODUCTION

Background

The increasing level of consumption of DS in the U.S. in the last two decades has drawn the attention of regulatory agencies, researchers and healthcare professionals. The United States is leading the world in DS consumption across all segments of the population.[1-3] Between 1999 and 2002, approximately 57% of women and 47% of men in the U.S. reported using some type of DS in the past 30 days.[4, 5] In addition, the market of DS is growing to be a billion dollar industry with sales of $23.7 billion in 2007.[6] These DS include substances such as vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, and metabolites.[7] This definition is comprehensive and includes wide variety of supplements that are very different in their effectiveness and safety for human consumption. While some of these DS are effective and safe, there are many safety concerns associated with the use of some others. For example, Ginkgo biloba has been implicated in the occurrence of an epileptic seizure, and chronic use of zinc may result in anemia.[8]

In addition, some potentially dangerous interactions between DS and drugs have been described in the literature. These interactions could be synergistic effects, poisoning, or inactivation of one of the substances. For instance, St. John's Wort that is used to enhance mood may interact with several narrow therapeutic range drugs that are metabolized through the liver.

These interactions are mediated through the ability of St. John's Wort to induce liver enzymes of the cytochrome P450 system. St. John's Wort may also increase the toxicity of some antidepressants and compromise the effectiveness of some anticonvulsants and HIV antivirus drugs.[9, 10] Garlic, ginger, and Ginkgo biloba may increase risk of bleeding when used with anticoagulants.[11]

The effectiveness of many individual DS products and combination DS products is not known. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, the U.S. Food and Drug Administration (FDA), unlike new prescription and over-the-counter drugs, does not require premarketing efficacy and safety assessments of DS.[7, 12] Only after a DS product reaches the market is the FDA responsible for taking action against any product proven to be unsafe. It is the responsibility of the DS manufacturer to ensure the effectiveness and safety of their products. DS manufacturers are, however, obligated to follow the current good manufacturing practices (cGMPs) for DS. These practices require proper control of DS so that they are processed in a consistent manner and meet quality standards.[13] FDA considers DS as generally safe unless proven otherwise through its Adverse Event Reporting System (AERS). If there are signals of a health concern, FDA conduct further investigations through literature review, clinical data analysis, or conducting clinical studies to confirm the health concern. After confirmation, FDA takes safety actions including warning consumers and healthcare professionals, requesting recalls or even stopping the importation or manufacturing of a DS product.

According to DSHEA, DS manufacturers are not required to report adverse events to FDA. It was not until 2006 when congress passed the Dietary Supplements and Nonprescription

Drug Consumer Protection Act (DSNDCPA) stating that the manufacturing party, defined as manufacturer, packer, distributor and retailer if appears on the label as distributer, is responsible for reporting all serious adverse events associated with their products to the FDA MedWatch system within 15 business days.[12] The report must be submitted using a MedWatch form accompanied by a copy of the label of the marketed DS product. Additionally, healthcare professionals and consumers may voluntarily report serious and non-serious adverse events related to DS to the FDA MedWatch system.[14] The literature shows that most of the time healthcare professionals do not seem to report adverse events related to the use of DS so a majority of the adverse events probably go unreported to the FDA.[15] Contributing to this underreporting may be the assumption that most DS are considered safe by consumers and healthcare providers.[16] Other factors that might affect healthcare professionals' reporting patterns of adverse events related to the use of DS are age of the professional, years of experience, knowledge about DS and understanding of the reporting process of an AE.[17, 18] Identifying which factors affect the decision to report an AE could be helpful for authorities and administrative personnel in developing educational programs to improve the awareness of consumers and healthcare professionals about regulations of DS.

Among healthcare professionals, community pharmacists play an important role in the field of DS safety given the over-the-counter sale of these products in the community. They could be among the first line in detecting and reporting adverse events related to the use of DS. Moreover, DS consumers consider pharmacists as reliable and knowledgeable source of information and advice about DS. In a U.S. study, 37% of respondents viewed pharmacists'

advice for complementary and alternative medicine (CAM) as important and 30% of them relied on pharmacists as a source of information about the choices of DS and herbal products.[19]

Conjoint analysis (CA) and discrete choice experiments (DCE) are different methods that have been used to measure the importance of factors involved in making a personal judgment or a preference among alternatives. In the last two decades, CA has been increasingly used in medical research. This technique combines both experimental designs and survey designs in which scenarios are used to determine attributes influencing respondents' preferences or decisions in performing some action.

It is hypothesized that the decision of a pharmacist to report a DS related AE might be influenced by various attributes that are related to the patient, DS, concomitant drugs, severity of outcome, practice setting and availability of DS information resources and characteristics of practicing pharmacist.

Objectives and Hypothesis

As described in the conceptual framework in Figure 1.1, there are three objectives for this project:

1. ***Determine the importance of selected attributes that influence a pharmacist's decision to report a DS related AE.***

   Hypothesis 1: Age of the patient is an important attribute influencing pharmacists' decision to report a DS-AE.

Hypothesis 2: Time since initiation of dietary supplement is an important attribute influencing pharmacists' decision to report a DS-AE.

Hypothesis 3: Time since last change of drug therapy is an important attribute influencing pharmacists' decision to a DS-AE.

Hypothesis 4: Evidence of the AE in the literature is an important attribute influencing pharmacists' decision to report a DS-AE.

Hypothesis 5: Level of outcome of the AE is an important attribute influencing pharmacists' decision to report a DS-AE.

2. ***Describe practicing pharmacists' attitudes toward DS, knowledge about DS and understanding of their regulations, practice setting***
3. ***Describe the availability, usage and usefulness of common DS information resources.***
4. ***Determine the effect of pharmacist's characteristics (objective 2) on the importance of the selected attributes that influence a pharmacist's decision to report a DS related AE (objective 1)***

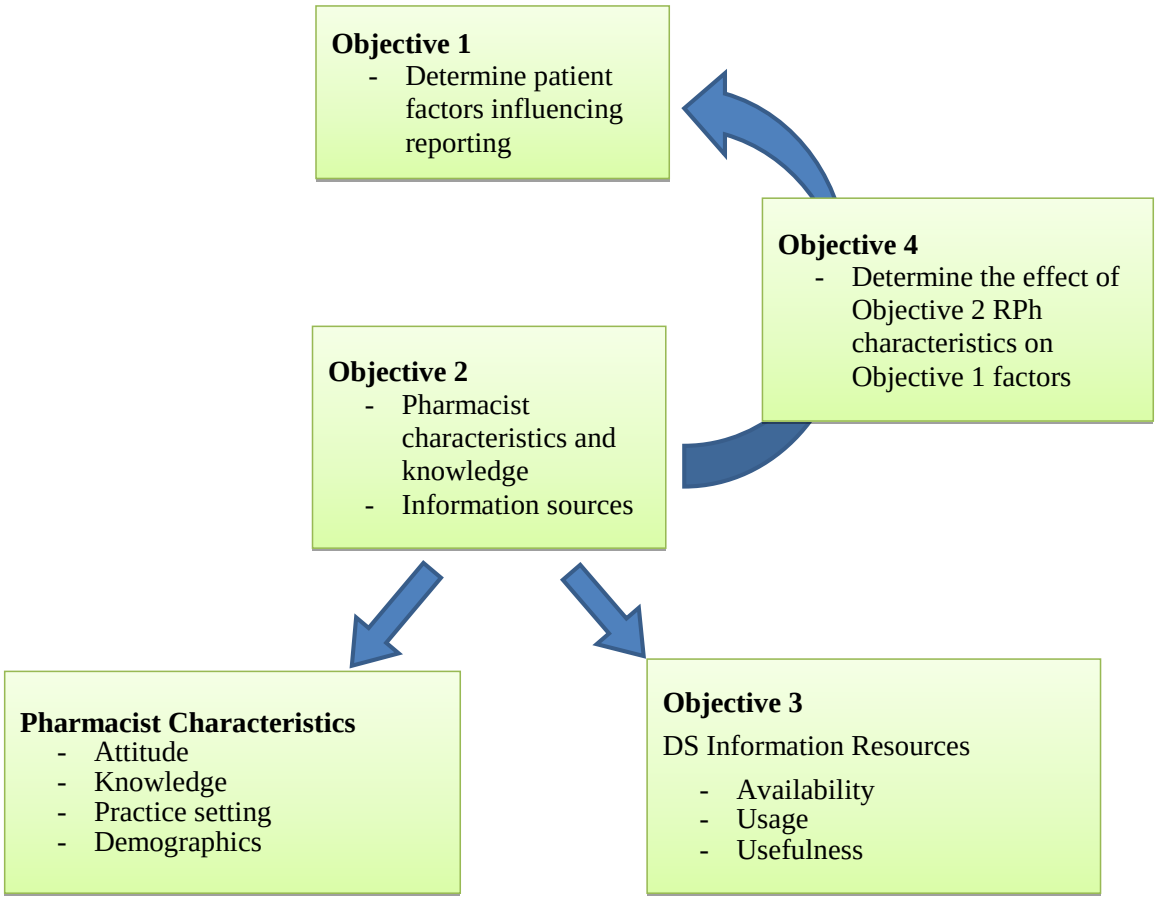


Figure 1.1 – The conceptual framework of project objectives

Significance

As mentioned before, FDA does not require premarketing safety and efficacy assessment of DS and considers them as generally safe unless proven otherwise through its MedWatch system. Unfortunately, the reporting rate of adverse events related to DS by consumers and healthcare professionals to the MedWatch system is low given their high consumption rate in the United States. Healthcare professionals should play an important role in this reporting process given their role in detecting and reporting of adverse events related to DS and in educating consumers about adverse events. Only about 20% of AERS reports were submitted by healthcare professionals. There are many possible factors contributing to such low reporting rate of adverse events related to the use of DS by healthcare professionals. Knowing which factors influence pharmacists' decisions to report DS related AEs might be helpful for authorities when establishing policies and regulations of the reporting process for adverse events in order to improve the detection of safety concerns for DS. It might be helpful for administrative personnel, as well, when developing educational programs to improve healthcare professionals' and consumers' knowledge about DS. This study focuses on pharmacists but it could be used as a foundation for future studies to evaluate factors affecting other healthcare professionals in reporting DS related AE.

CHAPTER 2 LITERATURE REVIEW

Dietary Supplements

Complementary and alternative medicine (CAM) as defined by the National Institutes of Health (NIH) is "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[20] Dietary supplements (DS) are considered to be CAM products. While many products fall into the DS category, the most commonly consumed DS are vitamins, minerals and herbals.[4] The term "dietary supplement" as defined by Congress in the Dietary Supplement Health and Education Act (DSHEA) of 1994, is "a product taken by mouth to supplement the diet that contains substances like vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites." A DS is intended for ingestion by humans in the form of a capsule, powder, softgel, or gelcap, and not in a form of injectable products or a conventional food or diet.[7] "Botanicals" is a synonym commonly used to refer to herbal remedies containing a plant or part of a plant used for its flavor, smell or therapeutic properties. The FDA regulations concerning DS differ from other dietary products. Before DSHEA, there was no formal definition of DS and the FDA had the authority to regulate them in a similar manner as diet, food additives or drugs.[21, 22]

Use of Dietary Supplements

The prevalence of DS use varies widely. The 2002 Health and Diet Survey sponsored by the FDA estimated that 73% of U.S. adults aged 18 years or older who spoke English and resided in households with telephones used a DS in the past 12 months.[3, 23] Based on National Health and Nutrition Examination Survey (NHANES) III database (1999-2002), about 57% of women and 47% of men in the U.S. reported using some type of DS in the last 30 days.[4, 5] The 1999-2002 NHANES III, showed that about 32% of children used DS regularly. A previous study using the 1976-1980 NHANES II indicated that the prevalence of regular use of DS among children varied from 42% for 1- to 2-year-old children to as low as 10% for 11- to 19-year-old males. Infants younger than 1 year were the lowest and 4- to 8-year-old children were the highest (12% and 48%, respectively).[24] In a recent cross-sectional study, almost 50% of older adults aged 57-85 years old used at least one DS during 2005-2006.[25]

Patients with various chronic diseases reported high prevalence of DS use.[26, 27] About 63% of patients with hypertension or hypercholesterolemia, 61% with coronary artery diseases and 53% with diabetes mellitus reported use of at least one DS in the last month.[27] Among prescription drug users, 52% used DS concomitantly with prescription drugs.[25]

The average use of DS among healthcare professionals has been suggested to be as high as or higher than the average use in the general population with about 81% of healthcare professionals enrolled in an online course reported using a vitamin, mineral, or other non-herbal DS and 51% of them reported using an herbal DS in the last week.[28, 29] Another study showed that about 53% of practicing Minnesota pharmacists reported personal use of DS.[16]

Nonvitamin/nonmineral (NVNM) products are a subcategory of DS that includes amino acids, herbs, or other botanicals. In 2007 the National Health Interview Survey (NHIS) assessed the past use (in the past 12 months) and the current use (in the past 30 days) of NVNM DS. About 18% of adults in the U.S. said they used some type of NVNM DS in the past 12 months and 13% in the past month. The most commonly used NVNM DS were fish oil/omega-3 (38.9%), glucosamine (21.9%), echinacea (17.3%), flaxseed oil or pills (15.7%), chondroitin (12.1%), ginseng, Ginkgo biloba, and garlic (about 11.0% each).[3] The 2002 Health and Diet Survey estimated that 42% of U.S. adults used herbs, botanicals, or other NVNM supplement in the past 12 months.[23] The NHIS estimated the use of NVNM in U.S. adults during 2000 to be about 15% at any time in the past year and 6% daily at the time of the survey. The most commonly used NVNM DS in this NHIS study were echinacea (30.3%), Ginkgo biloba (23.2%), garlic pills (15.7%) and ginseng (15.7%).[1] In 2000, the prevalence of use of NVNM was estimated by the National Center for Health Statistics of the Centers for Disease Control and Prevention to be 14.5% in the past year and 6.0%in every day.[1]

After the enactment of DSHEA in 1994, the estimated sales of DS including herbal products in the U.S. was $8.8 billion and increased to $15.7 billion in 2000.[30] According to a 2009 report of the U.S. Government Accountability Office (GAO), total estimated DS sales increased from 14 billion in 1997 to 23.7 billion in 2007, as shown in Figure 2.1. [6]

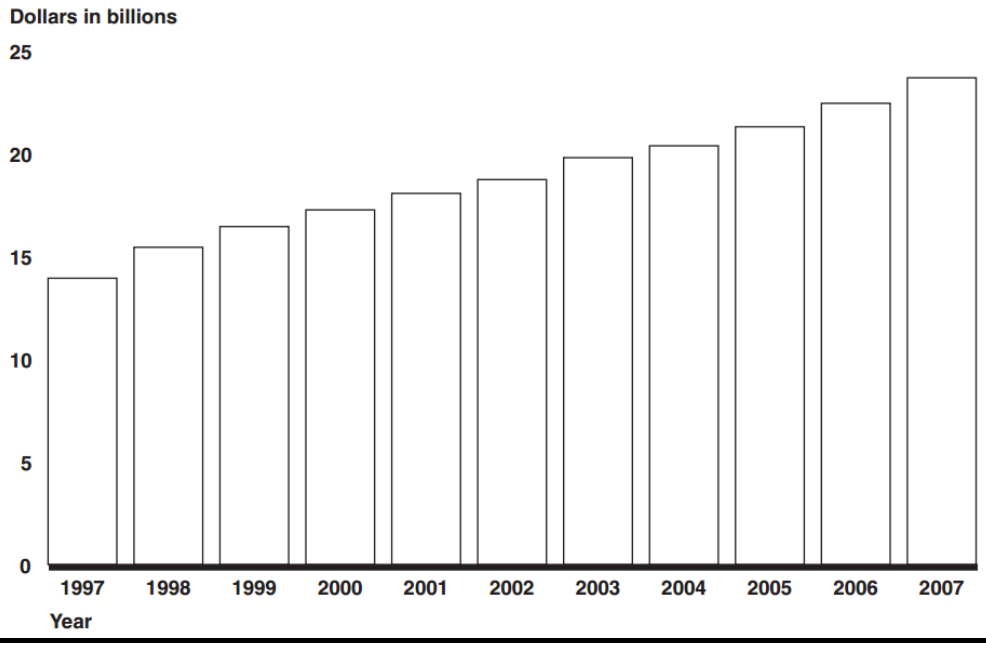


Figure 2.1 – Total Sales of DS in the U.S. from 1997 through 2007. (reference 6)

Regulations of Dietary Supplements

Regulation of DS passed several events overtime as listed in Table 2.1. In 1994, the U.S. Congress passed the Dietary Supplement Health and Education Act (DSHEA). Before DSHEA, FDA has the authority to regulate DS as food additives and drugs. With that, FDA could require DS manufacture to provide evidence of safety and efficacy of their products before it reach the market. However, that could have greatly reduced consumer access to potentially beneficial DS products. To allow a greater access, DSHEA was passed with clear definition of DS that distinguished them from food additives and drugs.[22]

Under DSHEA, FDA does not require safety and effectiveness approval of DS product before being marketed to consumers as it does for drugs. If the DS product contains a "new dietary ingredient" (NDI), an ingredient that was not marketed in the U.S. before October 15, 1994, the manufacturer may be required to notify FDA at least 75 days before marketing the product, depending on the history of use of the new ingredient.[7, 12] DSHEA also requires that certain information appear on DS labels in "Supplement Facts" panel. A structure-function disclaimer must be on DS labels that make structure-function claims such as "Calcium builds strong bones". The disclaimer says: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease". The FDA neither approves DS products nor conducts investigations to ensure the safety and effectiveness of these products before they are sold to consumers. This responsibility is placed on the DS manufacturers; however, the FDA still has the authority to regulate and even ban a DS product from the market when FDA demonstrates a significant or unreasonable risk associated with the use of the product through its MedWatch surveillance system. For instance, the FDA issued a regulation that banned the sale of ephedra in 2004 due to unreasonable risk associated with the regular use of ephedra.[31]

In 2006, significant changes have occurred in the regulation of DS. In December 2006, the congress passed the Dietary Supplement and Nonprescription Drug Consumer Protection Act (DSNDCPA) that required manufacturers to submit reports of serious AE to the FDA MedWatch system within 15 business days. This act became effective in December 2007.[12] A serious adverse event, as defined in the act, included any health-related event that resulted in, for example, a death, life-threatening experience, inpatient hospitalization, birth defect, or which

required, based on reasonable medical judgment, a medical or surgical intervention to prevent these serious outcomes. Moderate or mild adverse events are not required to be reported to the FDA.[12, 32]

In June 2007, FDA established its Current Good Manufacturing Practices (cGMPs) for DS. These manufacturing practices provide guidance for DS manufacturers to ensure DS product quality and consistency to meet quality standards. The cGMPs apply to all domestic and foreign companies and require DS to be manufactured with consistent identity, purity, strength, and composition. The final rule of cGMPs became effective in June 2008.[13]

The Center for Food Safety and Applied Nutrition (CFSAN) in FDA was established after passing the Dietary Supplement and DSNDCPA with a major responsibility of ensuring that consumption of food and DS is safe to humans. This center monitors post-marketing safety of DS through voluntary DS adverse event reporting system. In addition, it monitors DS product information such as labeling, claims, and package inserts.[33]

DSHEA also requires the formation of an executive level Commission on Dietary Supplement Labels and an Office of Dietary Supplements (ODS) within the National Institutes of Health (NIH). The Federal Trade Commission regulates any type of advertising and marketing of DS on television, in print, or on the Internet, to ensure that false claims are not made.[34] In 2002, 34 commercial websites of herbal supplements that are used for cancer were evaluated to determine the degree of compliance with the DSHEA regulation of structure/function claims. The study reported that 92%, 89%, and 58% of these commercial websites discussed prevention, treatment, and cure of cancer, respectively. The majority of websites claiming cures for cancer

through herb use supplied no evidence to support these claims. Fewer than 40% recommended that consumers consult a doctor prior to their use of DS.[35]

DSHEA established the ODS in 1995 to strengthen knowledge and understanding of DS by evaluating scientific information, funding and supporting research, publishing research findings, and educating the consumers and healthcare providers about DS to ensure safely and enhance health for public.[36]

Table 2.1 - Key events in the regulation of dietary supplements

Event	Key event
1990	The Nutrition Labeling and Education Act of 1990 amended the Federal Food, Drug, and Cosmetic Act to require most foods, including dietary supplements to bear nutrition labeling.
1994	DSHEA amended the Federal Food, Drug, and Cosmetic Act to create a new regulatory, safety standard, labeling requirements, and other rules for dietary supplements. Under DSHEA, dietary supplements are generally presumed to be safe.
2002	The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 amended the Federal Food, Drug, and Cosmetics Act to require all food companies, including dietary supplements companies, to register with the FDA no later than December 12, 2003, to provide information on the name and address of the facility and, to some extent, the types of products they manufacture or sell.
2004	FDA was successful in banning ephedra after thousands of adverse events, including a number of deaths, and a lengthy legal process.
2006	The Dietary Supplement and Nonprescription Drug Consumer Protection Act amended the Federal Food, Drug, and Cosmetic Act to require dietary supplement companies that receive a serious adverse event report to submit information about the event to FDA
2007	FDA finalized its Current Good Manufacturing Practices regulations to establish quality control standards for dietary supplements. The final rule becomes effective on August 24, 2007, but companies have 10, 22, or 34 months from the effective date of the rule to comply, depending on company size.
2007	Serious adverse event reporting requirement for dietary supplement companies become effective on December 22.

Source: Adopted from reference 6

Safety and Efficacy of Dietary Supplements

The historical use of DS and herbals was considered as proof of safety of these products by some manufacturers and consumers. This assumption, however, is problematic considering the wide variability in the concentration of the active ingredients of these products, the hundreds of new products, the differences in the methods of preparations, and the lack of scientific evidence supporting their safety for human consumption. Relatively few products and health claims of DS have been demonstrated, in animal or human research, to be effective and safe. For instance, folic acid has been shown to be effective in preventing the certain birth defects.[37] Also, calcium and vitamin D supplements have been shown to be helpful in preventing and treating bone loss and osteoporosis.[38]

Despite the safe use of a certain DS in the past, there is a still potential risk of using DS. Mega dosing of even safe DS such as vitamins and minerals might result in direct toxicity to consumers. For instance, excessive use of calcium might lead to complication of kidney function and kidney stone formation. Excessive use of vitamin A intake has been linked to liver abnormalities and some central nervous system adverse effects.[39]

Contamination with toxins and carcinogens is another safety concern in some DS products. For example, in 1990 a combination product to promote sleep containing L-tryptophan (LT) was associated with epidemic potentially fatal eosinophilia-myalgia syndrome (EMS). This condition was defined the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report (MMWR) as a flu like condition associated with eosinophil (EOS) count ≥2000 cells/cm. (normal range is 50-250 cells/cm.). The association between LT and EMS was first described in 1989 when the New Mexico Department of Health and Environment (NMDHE) received data

concerning three women who were consuming LT and were experiencing severe myalgia and eosinophilia. Many people had EMS over the next few years and by August 1990 more than 1500 cases of EMS and 37 deaths were reported to the CDC. The explanation of this association was not clear. Several studies by CDC linked that to a contaminant occurring in LT batches at a manufacturing plant in Japan between October 1988 and June 1989. More than 60 different impurities that had been associated with cases of EMS were identified in the LT batches. In 1990, LT was banned from sale in the U.S.[40] Several Asian studies showed that about 20% of natural products in a random sample of hospitals were contaminated pharmaceutical including adulterants, caffeine, paracetamol, indomethacin, hydrochlorothiazide and prednisolone.[41]

The FDA banned the sale of ephedrine fat-burning products in 2003, because studies demonstrated that use of such product was associated with increased risk of heart palpitations, hypertension, and stroke.[42, 43] In May 2009, the FDA banned the sale of Hydroxycut, a product used to help burn fat, because its use was associated with nausea, vomiting, and liver injury.

Dietary Supplement-Drug Interactions

A recent survey found that about 31% of respondents reported taking herbal products with prescription drugs and 30% took DS with over the counter (OTC) drugs.[44] The interactions between DS and drugs, both prescription and OTC, could be potentially serious, especially among elderly. Several studies have identified potentially dangerous interactions between DS and drugs. That could be synergistic, poisoning, or antagonistic effects. In a Canadian study, 20% of children concurrently used conventional medications and natural health products (NHP). Theoretically possible NHP-drug or NHP-NHP interactions in the past 3 months were identified

in 16% children. Although many of the NHP-drug potential interactions are theoretical, few are as serious and potentially life threatening such as the interaction of warfarin and St. John's wort that is might result in potential bleeding.[45] St. John's wort, also, has been shown to reduce plasma levels of some drugs like cyclosporine, warfarin, and some statins.[46, 47] DS products often contain more than one ingredient that might interact with each other and might lead to severe adverse events.[48] A study by NIH showed that using St. John's Wort to enhance mood could significantly compromise the effectiveness of indinavir, which is an antiviral drugs often prescribed to treat HIV infection.[9, 11]

Patient Disclosure of DS Use Information

Disclosure of DS use to healthcare providers and factors influencing the disclosure is not well assessed. It is suggested that only 23% to 37% of CAM users disclosed at least one type of CAM use to their physician.[49, 50] For example, 69% of patients who use DS and prescription medication concomitantly do not disclose this information to their healthcare providers.[51]Although patients may not be forthcoming about DS use, healthcare practitioners similarly may not be asking about such use. Even when they do ask, patients may fail to inform them. A review study shows that about 70% of surgery patients who were taking DS failed to tell their doctors when asked.[49] In a recent study that assessed the changes in herb and DS use in the U.S. adult population between 2002 and 2007 using National Health Interview Surveys only 33.4% in 2002 and 45.4% in 2007 disclosed their herb or DS use to their healthcare professionals.[3]

Misperceptions about DS Regulations

Although the DSHEA has been in place for more than 18 years, research shows that consumers and healthcare professionals do not understand how DS are regulated. About 1,400 adults in the U.S. who had ever made a serious weight loss attempt were asked whether they believed weight loss DS were approved for safety by a government agency such as the FDA. More than half mistakenly reported that such DS were approved for safety by some government agency. The results were the same of those who used DS for weight loss and those who did not.[52] In another study, the knowledge about the FDA's role in regulating of DS was assessed on a convenience sample 262 of undergraduate students. The average score of a 12-item knowledge test was about 50%. The items were scored as 1 (True) or 0 (False).[53] In a recent study by the same team using the same instrument, undergraduate students were randomly assigned to one of three experimental conditions: the description of the DS stated that it had been approved by FDA in the first group, the description stated that it had not been approved by FDA in the second group, and nothing about FDA approval was included in the description in the third group. The average score of a 12-item knowledge test was about 50% in all of the three groups.[21]

Similar to consumers, healthcare professionals' knowledge about DS regulations is poor. The average baseline knowledge score about DS regulations of 335 physicians was 59% using a 5-item quiz as part of the study questionnaire. The average score dramatically improved after completion of an online learning module about DS to be 91%.[54] Kemper et al. administered a 28-item knowledge questionnaire to 1,268 healthcare professionals including physicians, nurses, dietitians, pharmacists, and students. The questions included items about the use, safety, and regulations of certain DS. The overall average score was about 66%. The average score was

significantly different when sub-classified by profession [(70%, 65%, 68%, 71%, and 61%; respectively); p <0.001].[55]

Dietary Supplement Information Resources

There are numerous information sources that healthcare professionals can consult to get information about DS. Access to these resources and reliability of the information is essential to provide informed advice to patients. These resources vary in their usefulness, ease of use, format, and frequency of update. These references include the Natural Medicines Comprehensive Database, Natural Standard (Natural Standard, Inc.), Review of Natural Products (a component of Facts and Comparisons 4.0), PDR for Herbal Medicines, and the web site of the National Center for Complementary and Alternative Medicine. Most of these resources have been reviewed in the literature.[56-62] None of these references are comprehensive and always up-to-date, and each of these has advantages and disadvantages. For these reasons, having access to more than one database or reference is important.

Nathan et al. surveyed 64 community pharmacists to examine the availability of information sources in the community pharmacy setting and to assess the attitudes of community pharmacists toward these resources. The frequency of use of these resources to answer questions was mainly seldom (48.4%) or often (n = 24; 37.5%). Few of them never used (n = 5; 7.8%) or always use (n = 4; 6.3%) these references. The most commonly available resources were the PDR for Herbal Medicines (42.5%), The Review of Natural Products (20.0%), and the web site of the National Center for Complementary and Alternative Medicine (12.5%). Respondents were mainly completely satisfied or somewhat satisfied (14% and 46.3% respectively).[61]

Out of the 116 poison information centers in the Untied Stated, 66 responded to a survey to assess the resources these centers are using to respond to DS information requests. The most commonly available DS resources were Facts and Comparisons' The Review of Natural Products (78.80%), the print version of Natural Medicines Comprehensive Database (78.80%), and Complete German Commission E Monographs (69.70%). Table 2.2 list the 10 most commonly available resources. The most commonly used DS resources were Web site of the National Center for Complementary and Alternative Medicine (36.40%), AltMedDex System (16.70%), The Review of Natural Products (16.70%). Table 2.3 list the 10 most commonly used resources.[62]

Table 2.2 – Most commonly available dietary supplement resources at 66 drug information centers

Resource	Availability %
The Review of Natural Products	78.8
Natural Medicines Comprehensive Database (print)	78.8
Complete German Commission E Monographs	69.7
PDR for Herbal Medicines	66.7
AltMedDex System	59.1
PDR for Nonprescription Drugs and Dietary Supplements	56.1
Tyler's Honest Herbal	51.5
Natural Medicines Comprehensive Database Web site	48.5
Herbs of Choice	37.9
PDR for Nutritional Supplements	30.3

Source: Adapted from reference 62.

Table 2.3 – Most commonly used dietary supplement resources at 66 drug information centers

Resource	Availability %
Natural Medicines Comprehensive Database (print)	36.4
AltMedDex System	16.7
The Review of Natural Products	16.7
Natural Medicines Comprehensive Database (print)	15.2
Professional's Handbook of Complementary and Alternative Medicine	3.0
Complete German Commission E Monographs	1.5
Other	1.5

Source: Adapted from reference 62.

Another study assessed the usefulness of 14 most common DS references that healthcare professionals use to answer DS related questions. The ability of references to answer all DS information requests that were submitted to participating drug information centers between April and September 2000 were scored on a 4-point scale. The most useful electronic references for providing information on DS were the Natural Medicine Comprehensive Database, Micromedex and The Natural Pharmacist website. The Natural Therapeutics Pocket Guide was the most helpful book reference.[57]

Consumers' Sources of Information and Advice about DS

Consumers of DS reported using a variety of information sources to gain knowledge of DS and to make their decision to use these products mostly without knowing the credibility and reliability of the information. These sources include healthcare providers, friends, media, and manufacturers of DS. Trained health professionals are not always the source of information that consumers use to start taking a DS.

A study measured the prevalence of herbal (non-vitamins/non-minerals) DS usage among university students, rationale for usage, and identified sources of DS information. About 26% of student reported previous use of herbal DS. The main source of information was friends and family (52%), followed by health food stores (43%), and magazines and newspapers (32%). Mostly reported reasons of use were to improve energy (61%), to promote weight loss (38.0%), to burn fat (36%), and inadequate diet (35%).

Herbold et al. surveyed a sample of athletic high school students to measure prevalence of DS usage, attitudes, sources of dietary supplement information, and physical activity. Of the

351 adolescents who completed the survey, 78% have used some type of DS. Seventy-five percent of them were introduced to DS by family or friends and 25% by a physician. Mostly frequently reported reasons of use were for good health (52%) and to provide energy (36%).[63]

Another by Neuhouser et al., surveyed 104 adults on DS to know the sources of health information about each DS they are using and their motivations of using it. Part of that study was an open-ended question about all their sources of health information during the past 5 years. In addition, for each DS participants were asked what source of information motivated them to start taking it. The most common source of information reported was physician or nurse (71%) followed by print media sources (50%), broadcast media (40%), and family and friends (27%). About half of multivitamins/multiminerals, vitamin E and vitamin C users decided to take the DS based on advice from family members and friends. The health reasons behind using DS were to feel better for multivitamins/multiminerals users, to prevent acute illnesses such as colds and flu for vitamin C users, and to prevent chronic diseases for vitamin E and calcium users.[64]

Pillitteri et al. assessed the prevalence of DS use for weight loss and examined the perception of its safety and efficacy by consumers. Study participants were asked whether they believed weight loss supplements were approved for safety by a government agency such as the FDA. More than half of the 1,444 adults in the in this study who had ever made a serious weight loss attempt incorrectly reported that weight loss DS were approved for safety by some government agency. This was true for those who use weight loss DS and those who did not.[52]

The accuracy of information regarding recommendations or advice for DS use is a very important factor to ensure safe and proper use of these products. Studies above show that the use

of DS is mostly not related to evidence-based product benefits. These studies also indicate the need for better and more reliable information sources for DS consumers.

Spontaneous Averse Events Reporting Systems

Definitions of adverse event (AE) vary, but in general an AE is an unintended, undesired, or harmful effect associated with the use of a drug, intervention, or DS.[17] The link between the DS and the AE could be established through the analysis of large number of AE reports. Spontaneous adverse event reporting systems are an approach used to capture post-marketing adverse events associated with the use of a drug, intervention, or DS. In the United States, FDA has developed the MedWatch system, which is a passive system, to identify post-marketing safety problems of drugs, biological products, and DS. The Center for Food Safety and Applied Nutrition (CFSAN) take responsibility for monitoring DS related AE through its Adverse Event Reporting System (AERS). FDA relies primarily on this system to generate signals of safety concerns that are then further assessed and analyzed. If there is an actual public health problem with a DS product, an appropriate safety action is taken against it. The MedWatch system has several limitations that reduce its ability to generate signals of safety concerns such as the low reporting rate of DS related AEs. An FDA report estimated that the agency receives less than 1% of all AEs associated with DS.[48] With such low reporting rate, FDA finds it difficult or even impossible to quickly and effectively identify the potential risk associated with the use of DS. A report from FDA in 2001 stated that AERS received only 2,547 DS related reports from 1994 to 1999 while more that 100 million consumers reported using DS during that period with 12% (11.9 million) of them having experienced adverse events.[48] The number of reports received by

FDA is low as compared with other systems such as poison control centers (PCCs). As shown in Figure 2.2 in 1999 those centers received 1,300 reports while FDA received only 460 reports of DS related AEs.[44] Because reporting to AERS is voluntary for consumers and healthcare professionals, they tend to report to local PCCs more that FDA.[44]

Another limitation is the poor quality of information in a large proportion of AERS reports. This reduces the usefulness of such information in research and drawing conclusions.[48] In 1999, the MedWatch system received only 400 reports of DS related AEs, of which medical records were not available in 38% of cases, ingredients could not be determined in 32%, and there was no patient follow-up available in 27%.[48] The usefulness of the MedWatch system for the detection of safety signals is questionable, and there have been calls for the creation of a better instrument.[65]

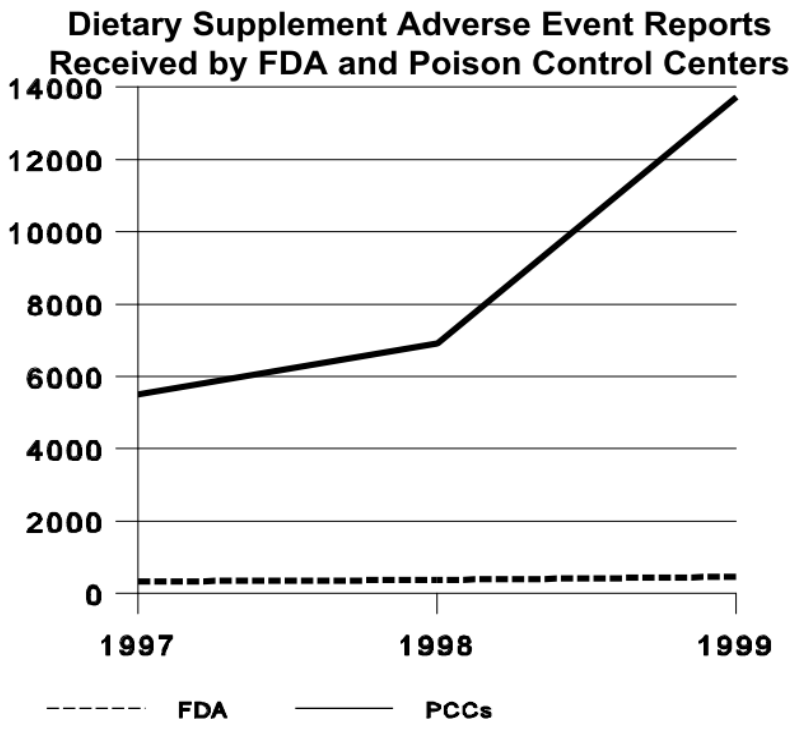


Figure 2.2 – Dietary Supplement adverse event reports received by FDA and PCCs from 1997 to 1999 (reference 44)
FDA: food and drug administration; PCCs: poison control centers

The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers (AAPCC) is another surveillance system that can be used to identify toxic exposure of any material including pharmaceuticals and DS. This system receives toxic exposure reports from all 60 PCCs in the U.S. and links it to the National Poison Data System (NPDS) database every 24 hours.[66]

PCCs have an essential role in the post-marketing surveillance of the safety of pharmaceuticals, herbs and DS is essential.[67-69] TESS database represents one potentially important source of information on consumer experiences with pharmaceuticals, herbs and DS. Starting from 2001, AAPCC began collecting data on botanicals reparably from DS. TESS data has been used in several studies on DS related AE.[67-69]

Of 2,784,907 substances involved in the 2,384,825 human poison exposure reports from the 60 participating United States PCCs filed in TESS in 2010, 71,545 (2.6%) exposures involved vitamins, 32,052 (1.2%) involved dietary supplements, herbs, botanical products, and homeopathic preparations and 10,720 (0.38%) were exposures to essential oils [66]

Like MedWatch, TESS is also a passive reporting system, such that reporting of any toxic exposures to the system is voluntary for public and healthcare professionals. For this reason, TESS likely undercounts the true number of toxic exposures to a product in the public. In addition, the accuracy of data entry may vary. Missing or inaccurate information is another limitation of this system. Because the information is transcribed from the telephone calls by individuals, who are often anonymous, TESS reports sometimes lack important data elements. In addition, not all calls represent toxic exposures, and sometimes the toxic effects are not confirmed to be necessarily caused by the exposure.[66] Sometimes, sensitive medical information

is not provided during the telephone calls from public or healthcare professionals, such that the accuracy and completeness of reporting may vary both by poison center and by case. The validity and usefulness of herbs and DS information in NPDS database is not confirmed and further research is needed in this area.[65]

Reporting of Dietary Supplements Adverse Events

Reports of DS related AEs are submitted to the FDA mainly by DS manufacturers, healthcare professionals, DS consumers, and PCCs. In a report commissioned by FDA, 20% of DS related AEs submitted to FDA came from healthcare professionals, and many were incomplete.[48] In order for healthcare professionals to report a DS related AE, the patient must reveal that he is using a DS and experiencing an AE; however, patients do not always report use of DS to their healthcare professionals as mentioned before.[51] Also, healthcare professionals believe they lack adequate information on how to detect and report DS related AE and recommend the need for additional training about DS.[70, 71]

According to the FDA, about 50% of the reports were submitted to the FDA by consumers. When consumers report an AE they usually do not inform or involve their healthcare providers. This results in missing relevant medical information in many reports submitted by consumers. FDA may find it difficult or impossible to determine causality. For instance, the FDA reviewer may find it difficult to draw causality from case reports that were filled by consumers for the adverse event of kava and ephedra because of missing details of the DS product and patient characteristics.[72-74] Consumers may lack information about DS regulation

and MedWatch system because of the limited role of FDA in communicating to the public regarding MedWatch system.[48]

PCCs reporting system (TESS) receives substantially higher numbers of DS related AE reports compared to FDA's MedWatch system.[66, 67, 75, 76] This may be because PCCs are located in hospitals and because of their higher visibility to the public and local healthcare professionals. In 1999, the TESS system received 1,300 DS related AE reports while FDA received only 460 reports (Figure 2.2). Only 1% of the reports received by TESS were reported to the MedWatch system.[44]

As mentioned earlier, reporting of any DS related AE was voluntary without regulation until the DSNDCPA became effective in December 2007. This act requires the manufacturing party to submit a report of all serious AEs to the FDA MedWatch system within 15 days of their being notified of the AE. Moderate or mild AEs are not required to be reported to the FDA.[12, 32] The 2001 FDA report noted that FDA was unable to determine the manufacturer of DS products for 32% of the products involved in reports.[48]

After DSNDCPA, number of DS related AE submitted to the MedWatch system saw a threefold increase compared with the previous year. In 2008, the MedWatch system received 1080 DS related AE compared to 350 in 2007 and 317 in 2006.[15, 48] Of the 1080 reports received in 2008, 662 were mandatory reports of serious AEs submitted by DS manufacturing party; the remaining 418 were voluntary reports including all mild, moderate and serious DS related AEs reported by consumers and healthcare practitioners to FDA.[15] As shown in Figure 2.3, FDA received more serious AE reports related to DS than previous years including 2003 and 2004 when several ephedra related AEs reports were submitted to FDA.[48] The implementation of the

DSNDCPA dramatically increased the number of DS related AE reports from DS manufacturers. As shown in Figure 2.4, the number of mandatory reports of DS related AE reports increased every month from January through December 2008 and these numbers were always more than voluntary reports.[15]

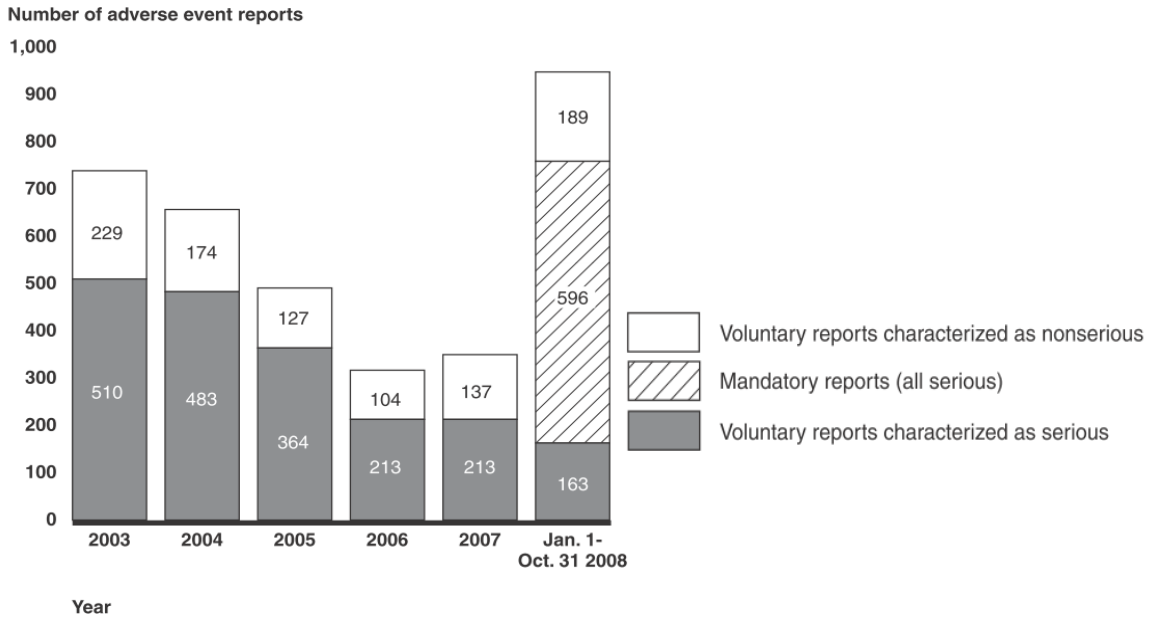


Figure 2.3 – The Number of DS-related adverse event reports to FDA MedWatch system from January 1, 2003, to October 31, 2008 (reference 48)
FDA: food and drug administration

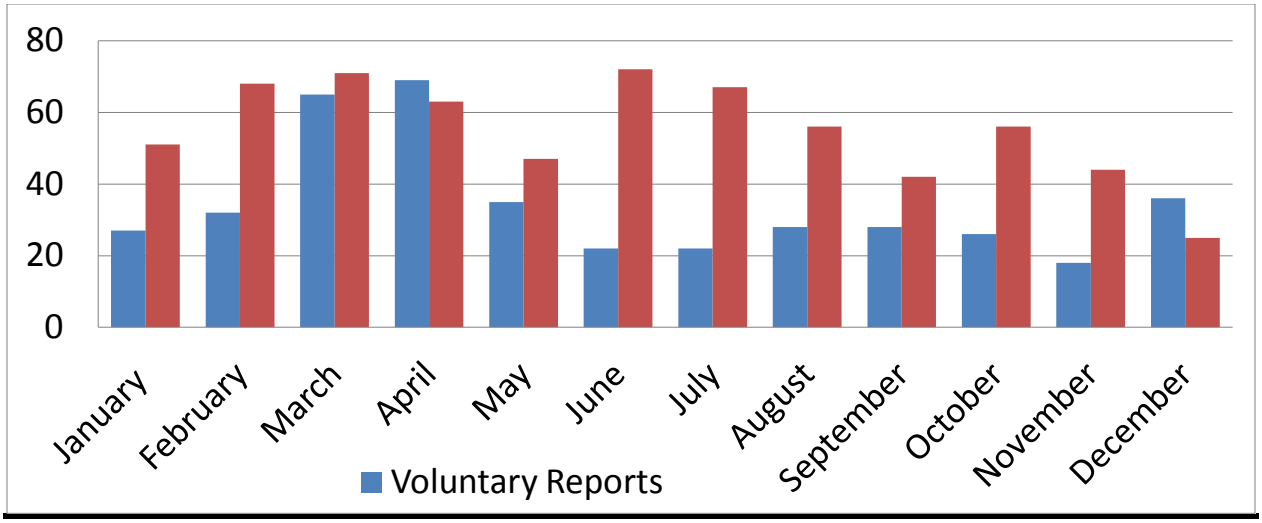


Figure 2.4 – The Number of DS-related adverse event reports to FDA MedWatch system from 2008 (reference 48)
FDA: food and drug administration

Reasons of Low Reporting Rate

Comparing the number of adverse event reports received and entered into AERS database related to DS and drugs and biologics from 2003, through 2007, clearly indicate the low reporting rate of DS related AEs, as shown in Table 2.4. There are several possible reasons described in the literature for such low reporting rate. Certain characteristics of DS may contribute to the low reporting rate of its AEs.[48] DS are "natural" products that are presumed to be safe by consumers, which may limit their willingness to link an AE with a "natural" product.[7, 17, 18] Also, DS are self-care products that consumers might choose to use without guidance or even knowledge of their healthcare professionals. Therefore, DS related AEs might be underreported.[44] Another possible reason low reporting rate DS related AE to FDA is that consumers might have perceived lack of FDA involvement after reading the FDA disclaimer on

DS products that says, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” Some consumers might think that FDA is not the right place to contact for any AE related to this product.

Table 2.4 – Comparison of the number of adverse event reports received and entered into FDA’s databases for review related to ds and drugs and biologics, 2003, through 2007

	Year						
Description	**2003**	**2004**	**2005**	**2006**	**2007**	**Total**	**Average**
Total dietary supplement reports recived and entred for review	739	657	491	317	350	2,554	511
Total drug and biologics reports recived and entred for review	226,217	273,601	323,384	337,155	364,449	1,524,806	304,961

Source: reference 48

Summary

In summary, reporting rate of serious and non-serious DS related AE to FDA is very low while their consumption is relatively high in the population. There are several potential AE that could be life threatening. The previous research to identify the reasons of such low reporting rate and how to overcome these factors is limited. In addition, factors considered in reporting a DA related AE could be different by profession. The research to understanding these factors is very

limited. Much is left to be done to better understand the effect of different variables on reporting rate of DS related AE and how to improve it. This study aims to investigate factors affecting practicing pharmacist's decision to report DS related AE.

CHAPTER 3 METHODS

Study Design

A cross-sectional survey design was used in this project to collect information about selected attributes in making the decision to report a DS related AE. A new survey was developed for the purpose of this project based on previous studies with similar objectives.[16, 28, 29, 54, 77-80]

Study Population and Setting

The study population was a convenience sample of pharmacists who were practicing and residing in the Commonwealth of Virginia as of October 2011. The sample was selected from a list of preceptors for PharmD students at the Virginia Commonwealth University School of Pharmacy. The list was composed of 764 practicing pharmacists at different locations in Virginia in a wide variety of practice settings. The list has information about each preceptor including the name, e-mail address, primary practice institution, and location. The use of a web-based questionnaire was determined to be beneficial over mailing paper questionnaires to facilitate participation from a range of practice settings that we have a handy access to it though the school

of pharmacy at Virginia Commonwealth University. There are several studies with reasonable response rate that used an online questionnaire in similar population.[81-83]

All practicing pharmacists and pharmacy residents who served as preceptors for at least one PharmD student at the VCU School of Pharmacy were eligible for this study. Practicing pharmacists working in academia, industry, consulting companies as well as other settings were eligible. This allowed for comparison of pharmacists in a variety of settings in order to best meet objectives of this study. The approval of the VCU Institutional Review Board (IRB) was obtained before starting this project.

Questionnaire Development

The development of the questionnaire involved several steps as illustrated in Figure 3.1. The preliminary paper version of the questionnaire was developed based on previous relevant research and expert opinion. At That version was pilot tested and the final paper version was created based on pilot test feedback and comments. The version was tested for technical issues and the final web-based version was then created. This web-based version of the questionnaire was created using the Qualtrics online survey software.[84]

A questionnaire composed of three sections was developed for the purpose of this project (Appendix B). The first section of the questionnaire presented four study scenarios consisting of different combinations of levels of the five attributes that were hypothesized to influence pharmacists' decisions on reporting AE related to DS. These four study scenarios were randomly selected from a pool of 56 possible scenarios. As illustrated in Figure 3.3, this section of the

questionnaire was unique for each participant and all other sections of the questionnaire were the same for all participants. This section also had one holdout scenario that was fixed for all participants. The participants were asked to indicate their decision to report the AE in each scenario on a 6-point ordered scale, ranging from 1 (Definitely not report) to 6 (Definitely report) for each of the following four questions: 1. How likely are you to report the above adverse event to the prescriber?; 2. How likely are you to report the above adverse event to the drug manufacturer?; 3. How likely are you to report the above adverse event to the dietary supplement manufacturer?; and 4. How likely are you to report the above adverse event to FDA MedWatch system?

In the second section of the questionnaire, set of questions were asked to measure responding pharmacists' attitudes regarding the clinical use and safety of DS, encountering a patient with possible DS related AE, places to report DS related AE, their reporting patterns of AEs to different agencies, as well as their knowledge about DS and DS regulations. In addition, a set of questions about DS information recourse availability, usage, and usefulness were asked.

The third section of the questionnaire contained a set of questions addressing demographics including age, gender, race and other characteristics of responding pharmacists including degree(s) earned, formal training related to DS or CAM, residency or fellowship, and current practice setting.

In this study, the FDA definition of DS was used, which is "an ingredient that is included in the DS definition in DSHEA, such as vitamins, minerals, and herbs or other botanicals that is intended for human consumption."[7] This definition was provided in the participant information sheet at the beginning of the questionnaire (Appendix A). DS manufacturer and drug

manufacturer is the “responsible person.” By law, they are required to document their contact information including the domestic address or phone number on the label of their products. That could be the manufacturer, packer, or distributor.[12, 85, 86] The drug manufacturer was used as one of the reporting places of the AE because patients in the scenarios were using concomitant drug therapy. Although the scenario described the patient as presenting with an AE that they were concerned was related to the DS, it is possible that participants attributed the AE to the drug therapy and not to the DS. Also, it is unclear whether pharmacists consider the DS manufacturer as an appropriate place for reporting AEs.

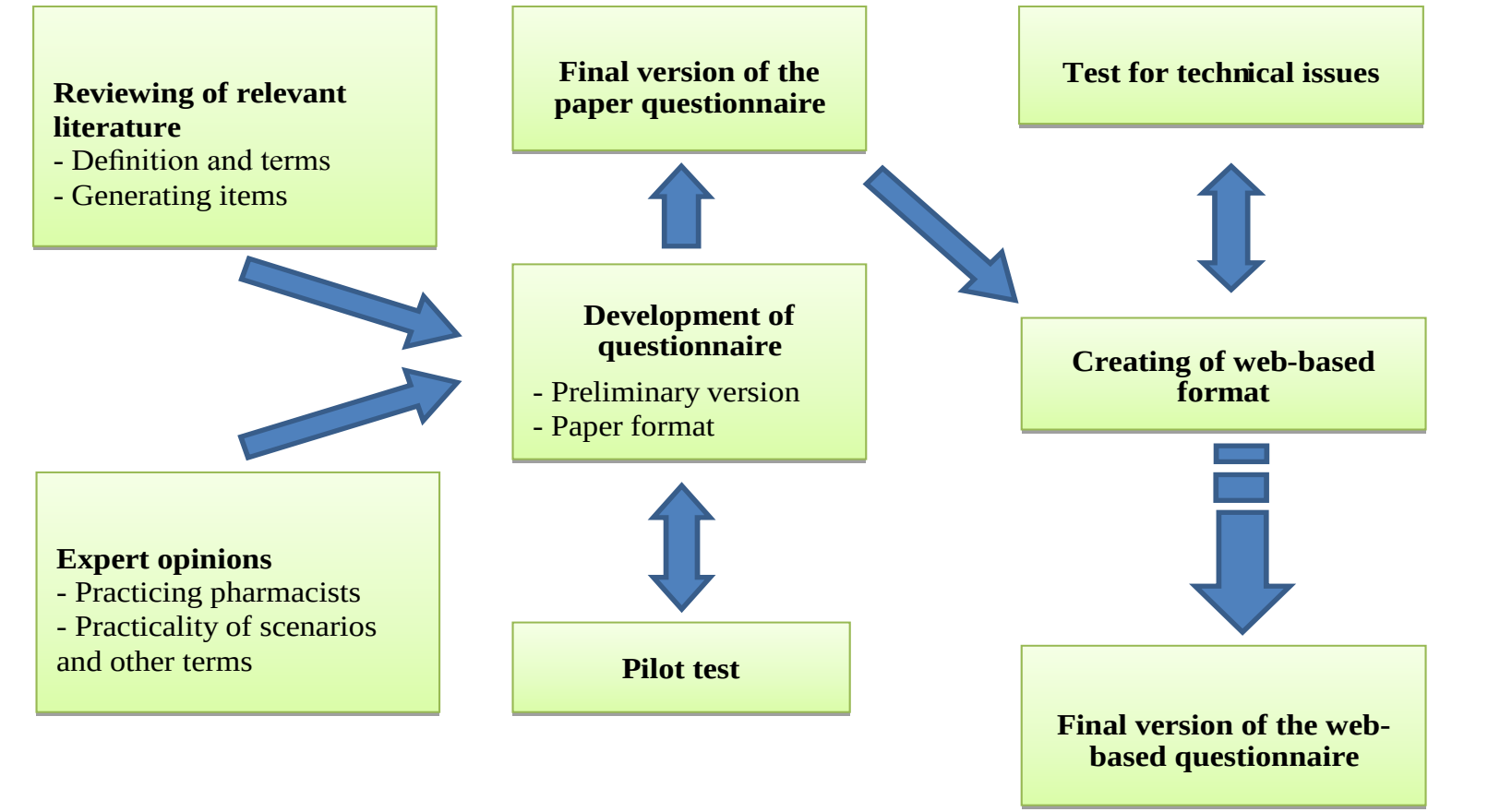


Figure 3.1 – Process of questionnaire development

Conjoint Analysis Exercise

Conjoint analysis (CA) was first introduced as a survey measurement method in 1964 in the field of mathematical psychology.[87] It was then adopted and used in marketing research and economics. It was used in these areas for multi-attribute modeling of consumer preferences and choice at the individual and aggregate level. Five stages are involved in conducting conjoint analysis: identifying the attributes, assignment of levels to each attributes, developing presentation scenarios, obtaining preferences and data analysis. This technique combines both experimental designs and survey designs in which scenarios are used to determine attributes influencing respondents' preferences or decisions in performing particular actions. The CA approach is generally similar to other methods that have been developed and used for understanding individuals' preferences among alternatives such as discrete choice experimentation (DCE), stated preference discrete choice modeling and vignette analysis.

In the last two decades, the technique of conjoint analysis has gained wide spread use in healthcare research to obtain the preferences of patients or individuals and communities in the delivery of healthcare services, determining optimal therapy options, managerial health decision making and as well as other applications.[88, 89] Its application to preference assessment in health care decision making is relatively new but there has been a substantial increase in publications reporting its use to evaluate health related preferences in the last decade, as shown in Figure 3.1.[90]

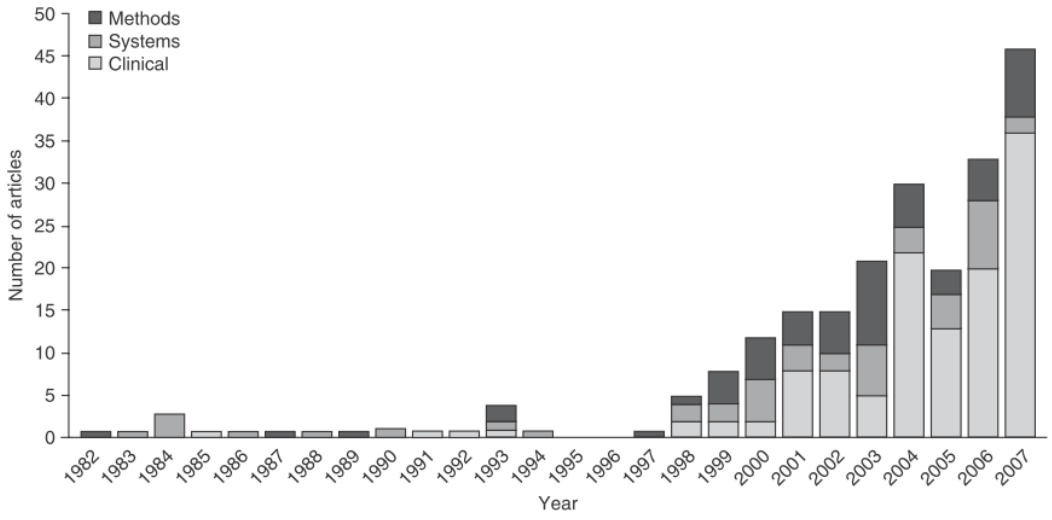


Figure 3.2 – Numbers of published articles, by thematic structure and year of publication, on conjoint analysis in the clinical literature. (reference 90)

In a recent study, this technique was used to identify important attributes of the decision to purchase influenza vaccine in the U.S. by asking a nationally representative sample of 251 medical office managers and physicians about their preferences for seven vaccine related attributes.[81] Another study used CA to evaluate how customers in Georgia selected a pharmacy to fill their prescriptions. A convenience sample of 175 consumers was surveyed, at four different pharmacy settings, on 26 attributes about "general pharmacy site features (16 items), pharmacist characteristics (5 items), and pharmacy staff characteristics (5 items)."[91] Kievit et al. used adaptive conjoint analysis (ACA), a computer-based choice-based conjoint analysis, to determine the influence of attributes related to rheumatoid arthritis activity on the decision of rheumatologists to provide specialized care to patients. The study was conducted on a convenience sample of 135 rheumatologists attending the annual meeting of the American College of Rheumatology. A total of six attributes (age of patient, initiation of DS, clinical symptoms, joint damage, disease activity, and current treatment) with three levels for each were used in this study.[92]

For the purpose of this study, highly relevant attributes and levels were selected based on literature review.[71, 93, 94] At beginning, six attributes were selected. Which were gender of the patient, age of the patient, time since initiation of the DS, time since last change of drug therapy, evidence supporting a DS related AE, and the outcome of the AE. However, after group discussion with practicing pharmacists, the gender of the patient attribute was deleted and instead gender was held constant in the scenarios to reduce the complexity of the scenarios. Also, the levels of time since initiation of the DS and time

since last change of drug therapy attributes reduces from three (1 weeks ago, 6 month ago, more than 2 years ago) to two (2 weeks ago and about 9 months ago). That is to allow sufficient time for the outcome of the AE to happen and to make the levels mutually exclusive. Both durations of 6 months ago and more than 2 years ago were considered as long durations in the preliminary testing so they were reduced into one duration of 9 months ago. As listed in Table 3.1, five final attributes were selected for the purpose of this study. The attributes and levels selected manifested 144 possible case scenarios ($3 \times 2 \times 2 \times 3 \times 4 = 144$). Instead of asking participants to evaluate all possible scenarios, a fractional factorial sample of scenarios was generated using the design of experiments function in SAS.[95, 96]

The minimum number of scenarios needed for estimation of the main effects of the five attributes and the interaction terms was 56 different scenarios. In addition, one holdout case scenario was created separately from study scenarios for the purpose of validation and reliability of the responses. The holdout case scenario was judged by all respondents but its responses were not included in the analysis to estimate the importance of each attribute. All these scenarios were created and entered into the Qualtrics survey website. Using the question randomization function of Qualtrics, four randomly selected scenarios were chosen for each participant from the pool of all 56 study scenarios (Figure 3.3).

Table 3.1 – Attributes and levels included in the conjoint analysis study

	Attributes	Levels
1.	Age of the patient	a. 25 years
		b. 45 years
		c. 70 years
2.	Time since initiation of dietary supplement	a. Within the past 2 weeks
		b. About 6 months ago
3.	Time since last change of drug therapy	a. Within the past 2 weeks
		b. About 6 months ago
4.	Evidence of dietary supplement adverse events	a. Consistent evidence in the literature
		b. Inconsistent (or mixed) evidence
		c. No evidence in the literature
5.	Outcome of the adverse event	a. Self-limiting and resolved upon discontinuation of dietary supplement
		b. Required outpatient/ER† visit
		c. Required hospitalization
		d. Resulted in permanent disability

ER: emergency room.

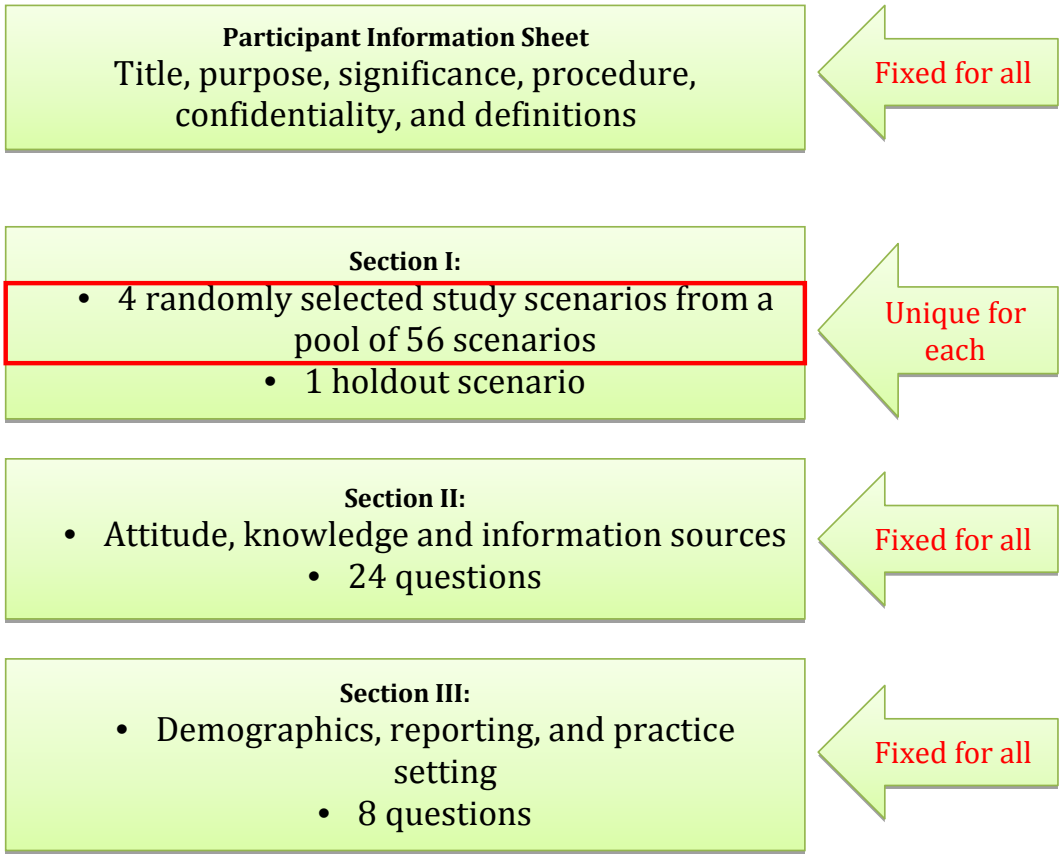


Figure 3.3 – Conceptual questionnaire design

Questionnaire Pretesting

The questionnaire was discussed and edited by the advisory committee. To assess feasibility and acceptability, a pilot test of the questionnaire was conducted with a group of pharmacy practice residents and fourth-year pharmacy students. In the pilot, test the following factors were considered: willingness of respondents to complete the questionnaire, the time required to complete the questionnaire, reasonable number of scenarios per questionnaire and the clarity of wording used in the questionnaire. The questionnaire was then revised based on feedback from the pilot test after discussion with the advisory committee.

Questionnaire Distribution

The Tailored Design Method involving multiple contacts with respondents to increase the response rate was used in this project.[82] A notification e-mail with a brief description of the study was sent to all eligible pharmacists to introduce the study. The e-mail contained a link to the web-based questionnaire (Appendix C). An information page presenting the purpose, procedure, significance, benefits and objective of the study was provided at the beginning of the questionnaire. Three "Thank You/Reminder" e-mails were sent to non-respondents two weeks, four weeks and five weeks after the notification e-mail (Appendix D). All "Thank You/Reminder" messages had a link to the web-based

questionnaire. An end of survey "Thank You" message was shown to all respondents. No incentives were offered for completing the survey.

Statistical Analysis

Objective 1 – Determine the importance of selected attributes that influence a pharmacist's decision to report an adverse event associated with the use of DS.

The responses from the 56 scenarios were used to estimate part-worth utilities of each level and the importance of each attribute. All of these variables were numeric variables measured on a 6-point ordered scale, ranging from 1 (Definitely not report) to 6 (Definitely report). There are four major dependent variables in this study representing the decisions of pharmacists to report an adverse event associated with the use of DS to the prescriber, the drug manufacturer, the DS manufacturer and the FDA MedWatch system. Each of these dependent variables was analyzed separately.

The independent variables included the levels of each attribute used in the particular scenario, as well as other variables of pharmacists' knowledge of DS and demographic characteristics. All independent variables from the scenario attributes were treated as categorical variables. Effects coding was used to represent the attributes levels using SAS experiment design tool. This is the recommended way of coding attributes in CA to allow estimations of both the main effects and interaction.[97] All possible interactions between the attributes were considered in the design phase.

To measure the adjusted associations of each of the four dependent variables and associated attributes, a separate linear regression model containing only the attributes as independent variables was built for each dependent variable. A random effects option was used in the regression models to account for the lack of independence of the responses as each participating pharmacist responded to four study scenarios. The results of the regression models were used to generate a utility score (part-worth) for each attribute level and importance values, which are measures of how important each attribute was to the overall preference. These importance values were calculated by dividing the range of the utility scores for each attribute separately by the overall utility scores ranges for all attributes. The values thus represent percentages and have the property of summing to 100.

As a check of validity of the utilities values, the differences between the observed and predicted preferences for the holdout scenarios was also measured and compared to the study scenarios.

Objective 2 – Describe practicing pharmacists' attitudes toward DS, knowledge about DS and understanding of their regulations, practice setting.

Objective 3 – Describe the availability, usage and usefulness of common DS information resources.

Descriptive statistics including the mean and standard deviation (SD) or median and 25th and 75th percentiles (interquartile range) for continuous variables or proportion

with 95% confidence intervals (CI) for categorical variables were calculated for attitudes, knowledge, demographic and other characteristics. Chi-squared tests for dichotomous variables, ANOVA for categorical variables with more than two levels, and two tailed Student's t-tests for the continuous variables were used to test for differences.

In order to score the two knowledge quizzes of DS and DS regulation, each correct answer was given a (1) and an incorrect answer or no answer was given a (0). Once all the answers were scored, each participant's totals were added and divided by the total possible correct answers. The total score was stated as a percentage.

Objective 4 – Determine the effect of pharmacist's characteristics (objective 2) on the importance of the selected attributes that influence a pharmacist's decision to report an adverse event associated with the use of DS (objective 1)

To estimate the effect of pharmacists' attitude, knowledge, demographics and other characteristics on their decisions to report, those variables were included as covariates in each of the four previously built models. Dummy variables were created for all categorical variables and they were included in each model to see if they changed the coefficients and part-worths for the profile attributes.

In all data analyses, two-sided P values <0.05 were considered as statistically significant. SAS® version 9.2 software (SAS® Institute Inc., Cary, NC) and Stata® release 12.1 for Windows (StataCorp LP, College Station, TX) were used to perform the statistical analysis.

Sample Size

Sample size calculation within CA studies is a controversial issue.[98] Previous CA studies that assessed decision preferences of healthcare professionals have used 150 respondents or less.[81, 89, 92] There are some "rules of thumb" which may be helpful in deciding the sample size for a conjoint analysis study.[98] For example one formula used in traditional choice-based CA suggests that:

$$\text{Sample Size} = \frac{(\text{Number of Attributes} - \text{Number of Levels} + 1) \times 100}{\text{Number of Tasks}}$$

In this study, the number of levels was five, total number of attributes was 14 and number of scenarios presented to each participant was five. Therefore, if this study were done using traditional full factorial choice-based CA, an adequate sample size for this study would be approximately 160 participants. However, this study used fractional factorial CA, which actually requires a smaller sample size.[96]

CHAPTER 4: RESULTS

This project was conducted using a convenience sample of all pharmacists who serve as preceptors for PharmD students in the school of pharmacy at VCU. As of October 2011, there were 764 preceptors at various institutions and locations. They were all contacted via email and asked to participate in the study. After the survey was e-mailed to the respondents, four reported no interest in participation and they were opted out from the reminder emails. E-mails to seven respondents were returned as "undeliverable" and one failed to be sent due to an incorrect e-mail address. This resulted in a total of 752 preceptors invited to participate in this study. This may not have represented the study population who actually received the e-mails as some of the preceptors might not have been active or they might have changed their institutions. A total of 272 participants responded to the questionnaire. Of these, 66 questionnaires were partially completed and were excluded from the analysis. Thus, the final total number of questionnaires included in the analysis was 206. The estimated response rate based on 206 completed questionnaires from a potential 752 active preceptors was approximately 27%.

Some of the variables were re-coded during the analysis. For instance, the "African American" category of the race/ethnicity variable was merged with the "Other" category because of low sample size. Also, the "health system inpatient pharmacy" and "health

system outpatient pharmacy" categories of the practice setting variable were merged together and all other categories except "community pharmacy" were merged with the "Other" category to allow comparison of the healthcare system and community practice settings. For some other comparisons, "health system outpatient pharmacy" and the "community pharmacy" categories of the practice setting variable were merged together to allow comparison of the inpatient healthcare system and community practice settings.

Participants' Demographic and Other Characteristics

Respondent demographic information is reported in Table 4.1. Participants were predominantly female (129 [63.86%]). The race and ethnicity self-reported distribution was 167 (83.09%) Caucasian, 20 (9.95%) Asian/Asian American/Pacific Islander, 10 (4.97%) African/African American, and 4 (1.99%) other. Participants' ages ranged primarily from 30-59 years (136 [81%]). Only a few were younger than 30 or older than 60 years. There were 134 (65.05%) participants who completed a Doctor of Pharmacy (PharmD) degree and 115 (55.82%) who completed a bachelor of science. Only a few had a graduate degree (27 [13.11%]). Approximately 32% finished a residency program after graduation; however, only few of them completed a fellowship after their residency (2%). About one fifth of the participants had formal training related to DS or CAM. The majority of the participants (95 [46.34%]) were working in a health system inpatient pharmacy or a community pharmacy (66 [32.20%]).

Table 4.1 – Participants' demographic and other characteristic

Characteristic (N)	Categories	Responses No. (%)
Gender (202)	Male	73 (36.14%)
	Female	129 (63.86%)
Race/Ethnicity (201)	Caucasian	167 (83.09%)
	African/African American	10 (4.97%)
	Asian/Asian American/Pacific Islander	20 (9.95%)
	Other	4 (1.99%)
Age category (203)	Younger than 30 years	25 (12.68%)
	30-39 years	56 (27.80%)
	40-49 years	55 (26.83%)
	50-59 years	52 (25.37%)
	60 years or older	15 (7.32%)
Degree(s)* (206)	Bachelor of Science (BS)	115 (55.82%)
	Doctor of Pharmacy (PharmD)	134 (65.05%)
	Graduate Degree	27 (13.11%)
Residency or fellowship (205)	Residency	65 (31.71%)
	Fellowship**	8 (3.90%)
	No	132 (64.39%)
Formal training related to DS or CAM (204)	Yes	42 (20.49%)
	No	162 (79.51%)
Primary practice setting (205)	Inpatient pharmacy	95 (46.34%)
	Community pharmacy†	66 (32.20%)
	Other††	44 (21.46%)

DS: dietary supplement; CAM: complementary and alternative medicine
* Overlapping; denominator is not the same for each category as this is a select all that apply responses
** 4 participants have completed both residency and fellowship
† Health system outpatient pharmacy was included in this category
†† This group includes home healthcare services, poison control center or drug information center, nursing home, skilled care or long- term care facility, ambulatory healthcare facility, academia

Reporting of Dietary Supplements Related Adverse Events

Approximately 40 percent of participants had encountered a patient with a suspected AE related to DS during their practice (Table 4.2). Table 4.3 shows the description of reporting patterns of DS related AE to FDA MedWatch system, drug manufacturer and DS manufacturer. Over half (110 [53.40%]) of the participants indicated that they had reported an AE to the FDA MedWatch system. However, only 8% included a DS in their reports to the MedWatch system. More participants had reported an AE to a drug manufacturer than to the MedWatch system. One hundred (48.54%) of the participants indicated that they had reported an AE to a drug manufacturer but never included a DS in their reports and 19 (9.22%) had included a DS in their reports. Unlike reporting to the MedWatch system and a drug manufacturer, reporting to a DS manufacturer was very limited. Only 11 (5.34%) had reported an adverse event to a DS manufacturer.

Table 4.2 – Encountered a suspected DS related adverse event

Characteristic (N)	Answers	Responses No. (%)
Encountered a patient with a suspected AE related to DS (206)	Yes	83 (40.29%)
	No	123 (59.71%)

DS: dietary supplement; AE: adverse event

Table 4.3 – Reporting of DS related adverse event to FDA MedWatch, drug manufacturer and DS manufacturer

Characteristic (N)	Answers	Responses No. (%)
Reported an AE to the FDA MedWatch system (206)	Yes, and I have included DS	16 (7.77%)
	Yes, but I never included DS	94 (45.63%)
	No	96 (46.60%)
Reported an AE to a drug manufacturer (206)	Yes, and I have included DS	19 (9.22%)
	Yes, but I never included DS	100 (48.54%)
	No	87 (42.23%)
Reported an AE to a DS manufacturer (206)	Yes, and I have included DS	11 (5.34%)
	No	195 (94.66%)

FDA: Food and Drug Administration; DS: dietary supplement; AE: adverse event

Attitudes Toward Dietary Supplements

Figure 4.1 and Table 4.4 show the description of the overall attitude the participants had toward the clinical use and the safety of DS. The overall attitude of the participants toward the clinical use of DS tended to be positive. A majority of the participants were positive or somewhat positive (67.50%). Table 4.4 shows the average attitude scores of participants toward the clinical use of DS considering the attitude score as a continuous variable ranging from 1 to 5 with 1 being the most positive score and 5 the most negative score. The average score of 2.90 (SD=1.09) was below the median of 3 (range=2-4) indicating a positive attitude.

On the other hand, the overall attitude of the participants toward the safety of DS tended to be negative. Over 40% of the participants were negative or somewhat negative regarding safety. Table 4.4 shows the average attitude scores of participants toward the safety of DS considering the attitude score as a continuous variable ranging from 1 to 5 with 1 being the most positive score and 5 the most negative score. The average score, 3.20 (SD=0.99) was above the median of 3 (range=2-4) indicating a negative attitude.

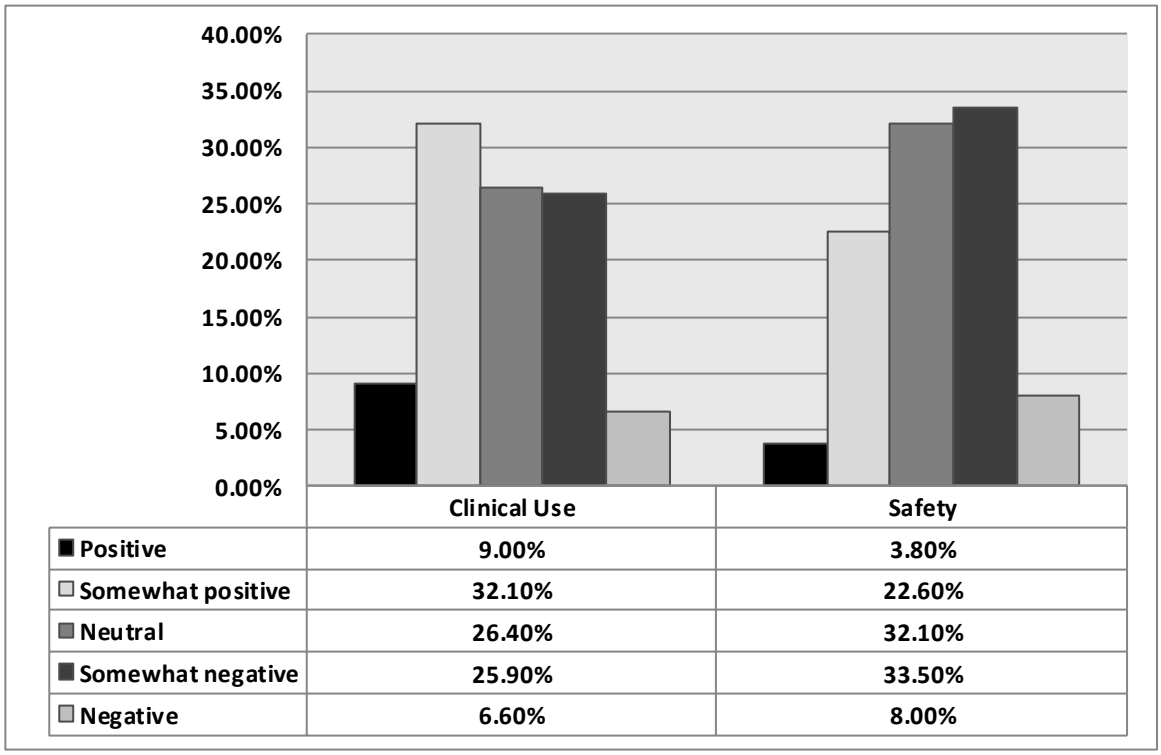


Figure 4.1 – Overall attitudes of participants toward the clinical use of DS and the safety of DS.

Table 4.4 – Average attitude scores of participants toward the clinical use of DS and the safety of DS

Attitude toward	No. of Responses	Mean* (SD)	Median (25%-75%)
Clinical Use	206	2.90 (1.09)	3 (2 - 4)
Safety	206	3.20 (0.99)	3 (2 - 4)

DS: dietary supplement; SD: standard deviation
* The mean of the five points scale responses when used as a continuous variable

The average attitude scores toward the clinical use of DS showed no significant differences by gender, age categories, or race (Table 4.5). However, there is some variability in the average attitude score toward the clinical use of DS. Females tended to have a more positive attitude than males. Also, the average attitude toward the clinical use of DS becomes more positive as age category increases except for the 60 years or older category. In participants under age 30 the average attitude score was 3.16 (SD=1.02) compared to 2.71 (SD=1.14) for participants aged 50-59 years. The mean was 3.13 (SD=1.25) for the 60 years or older participants. Asian/Asian American/Pacific Islander participants had a negative attitude score 3.10 (SD=0.79) compared to Caucasians with a mean of 2.94 (SD=1.12) and other races who scored 2.46 (SD=0.97). The only significant difference in the attitude toward the clinical use of DS was between those who did and those who did not have formal training related to DS or CAM after graduation ($p = 0.001$). The average attitude score for those who did have formal training was 2.40 (SD=1.19) compared to 3.03 (SD=1.04) for those who did not have formal training.

Table 4.5 – Relationship between respondent characteristics and the attitude towards the clinical use of DS

		Attitude toward the clinical use of DS	
	Categories	Mean (SD)	**p-value**
Overall		2.91 (1.09)	
Gender			0.309
	Male	3.00 (1.17)	
	Female	2.84 (1.04)	
Age categories			0.370
	Younger than 30 years	3.16 (1.02)	
	30-39 years	3.00 (1.01)	
	40-49 years	2.84 (1.10)	
	50-59 years	2.71 (1.14)	
	60 years or older	3.13 (1.25)	
Race/ Ethnicity*			0.235
	Caucasian	2.94 (1.12)	
	Asian/Asian American/ Pacific Islander	3.10 (0.79)	
	Other	2.46 (0.97)	
Formal training related to DS or CAM			0.001
	Yes	2.40 (1.19)	
	No	3.03 (1.04)	

DS: dietary supplement; CAM: complementary and alternative medicine; SD: standard deviation

* African American category was merged with "Other" category because of low sample size

The attitude toward the safety of DS showed no significant differences by gender, age categories, or races (Table 4.6). Participants of both gender categories and all age categories had negative average attitude scores related to the safety of DS. Both Caucasian and Asian/Asian American/Pacific Islander had a negative attitude compared to other races: 3.25 (SD=1.01), 3.35 (SD=0.81) and 2.77 (SD=0.83) respectively. The only significant difference in the average attitude toward safety of DS was between those who did and those who did not have formal training related to DS or CAM after graduation ($p = 0.009$). The average attitude score for those who did have formal training was 2.86 (SD=0.98) compared to 3.30 (SD=0.99) for those who did not have formal training.

Table 4.6 – Relationship between respondent characteristics and the average attitude responses toward the safety of DS

		Attitude toward the safety of DS	
	Categories	Mean (SD)	**p-value**
Overall		3.21 (0.99)	
Gender			0.746
	Male	3.23 (1.02)	
	Female	3.19 (0.97)	
Age categories			0.481
	Younger than 30 years	3.40 (0.87)	
	30-39 years	3.34 (1.01)	
	40-49 years	3.18 (0.96)	
	50-59 years	3.06 (1.09)	
	60 years or older	3.07 (0.70)	
Race/ Ethnicity*			0.204
	Caucasian	3.25 (1.01)	
	Asian/Asian American/ Pacific Islander	3.35 (0.81)	
	Other	2.77 (0.83)	
Formal training related to DS or CAM			0.009
	Yes	2.86 (0.98)	
	No	3.30 (0.99)	

DS: dietary supplement; CAM: complementary and alternative medicine; SD: standard deviation

* African American category was merged with "Other" category because of low sample size

Knowledge of Dietary Supplements

The average DS identification and DS regulation scores were used as continuous variables in all data analysis. The scores were also placed in categories of “0 to 20”, “21 to 40”, “41 to 60”, “61 to 80” and “81 to 100” on the basis of the percentage of questions answered correctly for better representation and description.

The results of both knowledge quizzes about DS identification and DS regulation are presented in Table 4.7, Figure 4.2, and 4.3. Participants’ knowledge about DS identification is better than their knowledge of DS regulation. The DS identification quiz was composed of 13 questions. Answers from 205 participants were considered in the analysis. One participant was dropped because of not answering any of the 9 questions. A total of 83 (40.30%) participants correctly answered all 9 DS identification questions. The mean (SD) score was 78.11 (24.21) as listed in Table 4.9. For better graphical representation of the DS identification and DS regulation scores, scores were placed in categories of “0 to 20”, “21 to 40”, “41 to 60”, “61 to 80” and “81 to 100” on the basis of the percentage of questions answered correctly. The histogram (Figure 4.2) shows the distribution of participants’ percentage scores on the DS identification quiz. The average scores were categorized into 5 categories of 20 points each for better description. As listed in figure 4.2, these categories are (0 to 20), (21 to 40), (41 to 60), (61 to 80), and (81 to 100). Almost one half of the participants fall in the highest score category (81 to 100) and only 13.17% fall in the lowest score categories (0 to 20) and (21 to 40). About 20% of respondents fall in the middle score categories (41 to 60 or 61 to 80)

The DS regulation quiz was composed of 13 questions. For the analysis of this quiz, answers from 205 participants were considered. One participant was dropped because of not answering any of the 13 questions. Only one participant correctly answered all 13 DS regulation questions. Three participants had a score of zero. The mean (SD) score was 46.45 (16.91) as listed in Table 4.7. The histogram (Figure 4.3) shows the distribution of participants' percentage scores on the DS regulation quiz. The average scores were categorized into five categories of 20 points each for better description. As listed in figure 4.3, the same five categories used in the DS identification quiz are used in this quiz. Almost one half of the participants fall in the middle score category (41 to 60) and only one falls in the highest score category (81 to 100). About 20% of respondents fall in the middle score category (41 to 60) and about 24% in the lowest score categories (21 to 40) and (0 to 20).

Table 4.7 – Description of participants' scores of the knowledge quizzes

Knowledge of	Mean (SD)	Median (25%-75%)	Range
DS Identification n= 206	78.11 (24.21)	80 (60 - 100)	20 – 100
DS Regulations n= 206	46.45 (16.91)	42.30 (42.30 – 53.84)	0 – 100

DS: Dietary supplement; SD: Standard deviation

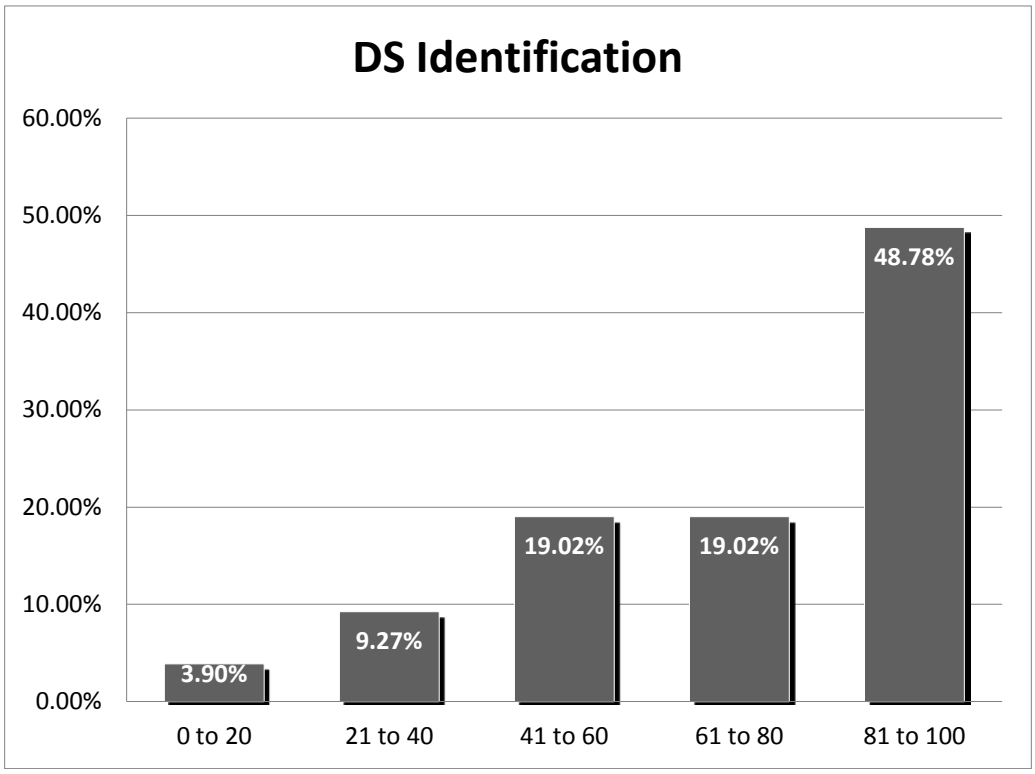


Figure 4.2 – Distribution of participants' average score of DS identification quiz

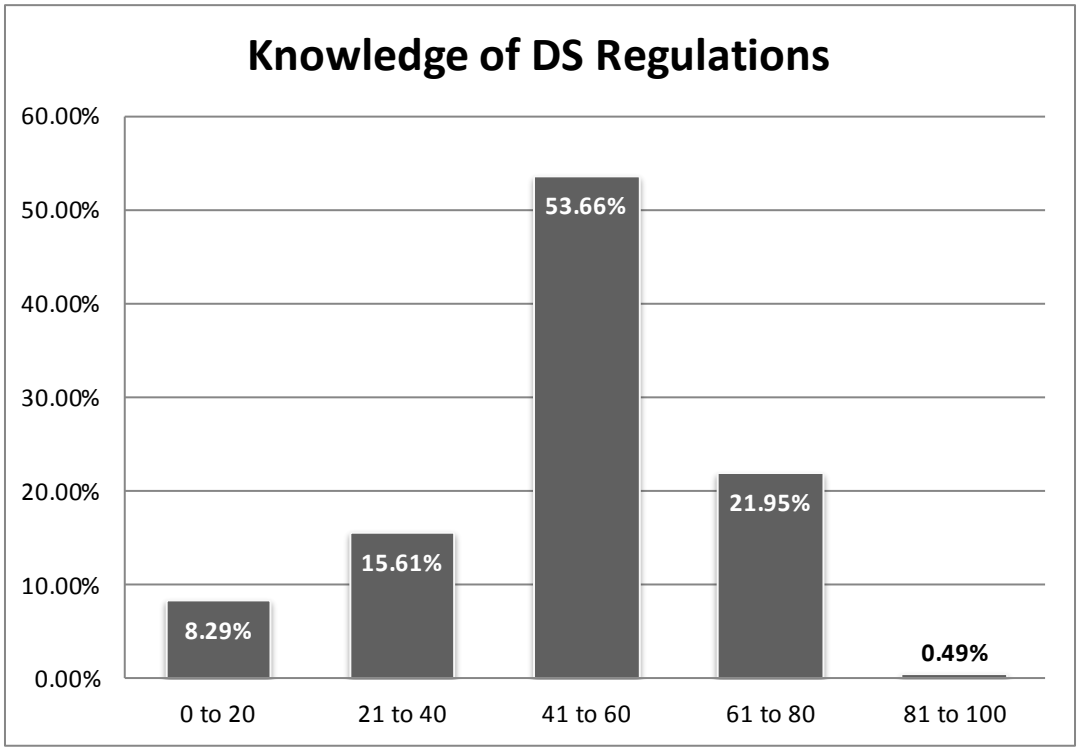


Figure 4.3 – Distribution of participants' average score of DS regulation knowledge quiz

The knowledge scores of DS identification and regulation were compared with attitudes toward DS safely and clinical use, formal training on DS or CAM, and practice settings (Table 4.10). There were no significant differences in the average DS identification scores by attitude toward the safety and the clinical use of DS. Participants with a positive attitude toward the safety of DS, however, had higher scores and those with negative attitudes had lower scores: 87.74 (SD=24.08) and 73.09 (SD=24.82), respectively. Similarly, participants with positive attitudes toward the clinical use of DS had higher scores than those with negative attitudes: 83.56 (SD=21.52) and 73.95 (SD=24.96), respectively. The average DS identification score was higher for those who had formal training related to DS or CAM than those who did not have formal training related to DS or CAM, 80.71 (SD=24.13) and 77.47 (SD=25.40), respectively. The average score of participants from health system practice settings was significantly lower than those from community settings: 73.14 (SD=25.32) compared to 83.39 (SD=20.56), respectively ($p = 0.009$).

Unlike the average attitude score of DS identification, the average scores of DS regulation were slightly higher in those with negative or somewhat negative attitudes toward both safety and the clinical use of DS. The average DS regulation knowledge score was higher for those who had formal training related to DS or CAM compared to those who did not have formal training treated to DS or CAM: 49.45 (SD=19.00) and 45.84 (SD=16.34), respectively. The average score of participants from healthcare system practice settings was lower than those from community settings: 45.46 (SD=15.65) compared to 48.83 (SD=15.71), respectively. There were no significant differences in the

average DS regulation scores by attitude toward the safety and the clinical use of DS, regardless of formal training in DS or CAM or practice setting.

Table 4.8 – Distribution of average knowledge scores by attitude, formal training and practice setting

Attitude	Categories	DS identification Mean score (SD)	p-value	DS regulation Mean score (SD)	p-value
Overall		78.11 (24.21)		46.45 (16.91)	
Overall attitude toward the safety of DS			0.162		0.182
	Positive	95.71 (7.87)		48.90 (9.08)	
	Somewhat positive	79.78 (24.08)		44.57 (15.76)	
	Neutral	79.56 (23.65)		44.63 (17.72)	
	Somewhat negative	75.59 (24.82)		47.96 (16.69)	
	Negative	70.59 (26.33)		51.81 (19.66)	
Overall attitude toward the clinical use of DS			0.203		0.442
	Positive	85.00 (18.55)		47.01 (18.02)	
	Somewhat positive	82.12 (21.52)		44.29 (14.54)	
	Neutral	74.26 (26.61)		43.95 (19.17)	
	Somewhat negative	76.48 (24.96)		50.93 (15.15)	
	Negative	71.43 (27.97)		48.35 (21.37)	
Formal training related to DS or CAM			0.442		0.220
	Yes	80.71 (24.13)		49.45 (19.00)	
	No	77.47 (25.40)		45.84 (16.34)	
Practice Setting			0.009		0.471
	Healthcare system	73.14 (25.32)		45.46 (15.65)	
	Community†	83.39 (20.56)		48.83 (15.71)	
	Other††	83.64 (23.83)		45.89 (21.09)	

DS: dietary supplement; CAM: complementary and alternative medicine; SD: standard deviation

† Health system outpatient pharmacy was included in this category to allow comparison between inpatient healthcare system and community practice settings

†† This group includes home healthcare services, poison control center or drug information center, nursing home, skilled care or long- term care facility, ambulatory healthcare facility, academia

Formal Training Related to Dietary Supplement

The results of subgroup analysis of the percentage distribution of those who did and did not have formal training related to DS or CAM are listed in table 4.11. Formal training is significantly different among practice setting ($p = 0.002$). The percentage of participants who had formal training is lower in healthcare system settings than in community settings: 36.6% and 43.9%, respectively. Also, formal training is significantly higher among those who encountered a patient with a suspected adverse event related to DS than those who had not: 54.76% and 45.24% respectively ($p = 0.027$). Formal training might have increased the awareness of participants in detecting adverse events related to DS. The reporting pattern to the FDA MedWatch system, drug manufacturer and DS manufacturer differed based on the presence or absence of formal training. Those who had training were more likely to report (50.00%) and to include a DS in their report (14.29%) to FDA MedWatch system than those who had not had training: 44.17% and 6.13%, respectively ($p = 0.002$). Similarly, those who had training were significantly more likely to report (52.38%) and to include a DS in their report (21.43%) to drug manufacturer than those who had not had training: 6.13% and 46.63%, respectively ($p = 0.002$). Also, those who had training were significantly more likely to report a DS adverse event to DS manufacturer than those who had not had training: 14.29% and 3.07%, respectively ($p = 0.011$).

Table 4.9 – Distribution of formal training related to DS or CAM by practice setting and reporting patterns

Variable	Categories	Formal training related to DS or CAM Yes (n=42)	No (n= 163)	p-value
Practice Setting				0.022
	Healthcare system	36.6%a	54.9%b	
	Community	43.9%a	22.8%b	
	Other	19.5%a	22.2%a	
Encountered a patient with a suspected AE related to DS				0.027
	Yes	54.76%	36.81%	
	No	45.24%	63.19%	
Reported an AE to the FDA MedWatch system (206)				0.106
	Yes, and I have included DS	14.29%	6.13%	
	Yes, but I never included DS	50.00%	44.17%	
	No	35.71%	49.69%	
Reported an AE to a drug manufacturer (206)				0.002
	Yes, and I have included DS	21.43%	6.13%	
	Yes, but I never included DS	52.38%	46.63%	
	No	26.19%	47.24%	
Reported an AE to a DS manufacturer (206)				0.011
	Yes	14.29%	3.07%	
	No	85.71%	96.93%	

DS: dietary supplement; CAM: complementary and alternative medicine; AE: adverse event; FDA: food and drug administration

Dietary Supplement Information Resources

Nine DS information resources were evaluated for their usage by participants, availability at practice site and usefulness as sources of information about DS. Usefulness was measured on a 5-point scale from 1 (not at all useful) to 5 (very useful). Usage, availability and usefulness are presented in table 4.12. The list of references is sorted according to their usage by participants. The top four most commonly used resources were Lexi-Comp® (69.90%), Facts and Comparisons: Review of Natural Products (61.65%), Natural Medicines Comprehensive Database (by Pharmacist's Letter) (57.77%), and Micromedex®: AltMedDex (47.57%). The Natural Therapeutics Pocket Guide was the least commonly used (7.28%). The top four most commonly available resources with Lexi-Comp® on top of the list (65.38%) followed by Natural Medicines Comprehensive Database (by Pharmacist's Letter) (62.41%), Facts and Comparisons: Review of Natural Products (56.87%), and Micromedex®: AltMedDex (50.67%). All of the resources were relatively useful with the minimum score of 3.03 and maximum score 4.21 out of 5. The most useful resource was Natural Medicines Comprehensive Database (by Pharmacist's Letter) followed by The Complete German Commission E Monographs and Facts and Comparisons: Review of Natural Products; 4.21 (SD=0.8), 3.96 (SD=1.06), and 3.9 (SD=0.95) respectively. The least useful resource was PDR for Herbal Medicines 3.03 (SD=1.24).

Table 4.10 – Description of DS information resources experience, availability and usefulness

DS Information resources	Ever Used n (%)	Availability n (%)	Usefulness Mean (SD)
Lexi-Comp®	144 (69.90%)	102 (65.38%)	3.61 (1.10)
Facts and Comparisons: Review of Natural Products	127 (61.65%)	91 (56.87%)	3.9 (0.95)
Natural Medicines Comprehensive Database (by Pharmacist's Letter)	119 (57.77%)	93 (62.41%)	4.21 (0.8)
Micromedex®: AltMedDex	98 (47.57%)	75 (50.67%)	3.86 (0.88)
PDR for Herbal Medicines	51 (24.76%)	30 (21.27%)	3.03 (1.24)
The Complete German Commission E Monographs	41 (19.90%)	15 (11.71%)	3.96 (1.06)
Natural Standard Herb & Supplement Guide	22 (10.68%)	17 (14.65%)	3.63 (1.45)
The Natural Therapeutics Pocket Guide	15 (7.28%)	7 (6.25%)	3.44 (1.15)
Other*	-----	13 (6.31%)	3.5 (1.53)

DS: dietary supplement: SD: standard deviation
*Other resources include: NIH website National Center for Complementary and Alternative Medicine, Memorial Sloan Kettering Electronic Database, Epocrates website, First DataBank, Clinical Pharmacology, package insert of supplement, Martindale's, Clinical Pharmacology Online.

Places to Report a Dietary Supplement Related Adverse Event

The percentage distribution of participants' self-reported opinion on places to report DS AE is described in Figure 4.4. The total number of responses is more than the total participants as they are responses to check all that apply. More than 90% of participants responded that they would report a DS AE to the prescribing healthcare provider. Reporting to FDA MedWatch system was the second highest followed by reporting to a DS manufacturer and to an internal safety review office; 86.34%, 53.17%, and 42.44% respectively. The analysis of percentage distribution of places to report a DS AE by practice setting is reported in table 4.13. Reporting to the prescribing healthcare provider and to DS manufacturer was not significantly different by practice setting. However, reporting to an internal safety review office ($p < 0.001$) and to the FDA MedWatch system was significantly different by practice setting ($p = 0.008$). The percentage of participants indicating an internal review office as a place to report a DS AE was significantly higher in healthcare system settings than in community or other practice settings; 70.10%, 12.60%, and 17.20% respectively. Similarly, the percentage of participants indicating the FDA MedWatch system office as a place to report a DS AE was significantly higher in healthcare system setting than in community or other practice setting; 52.50%, 23.70%, and 23.70% respectively.

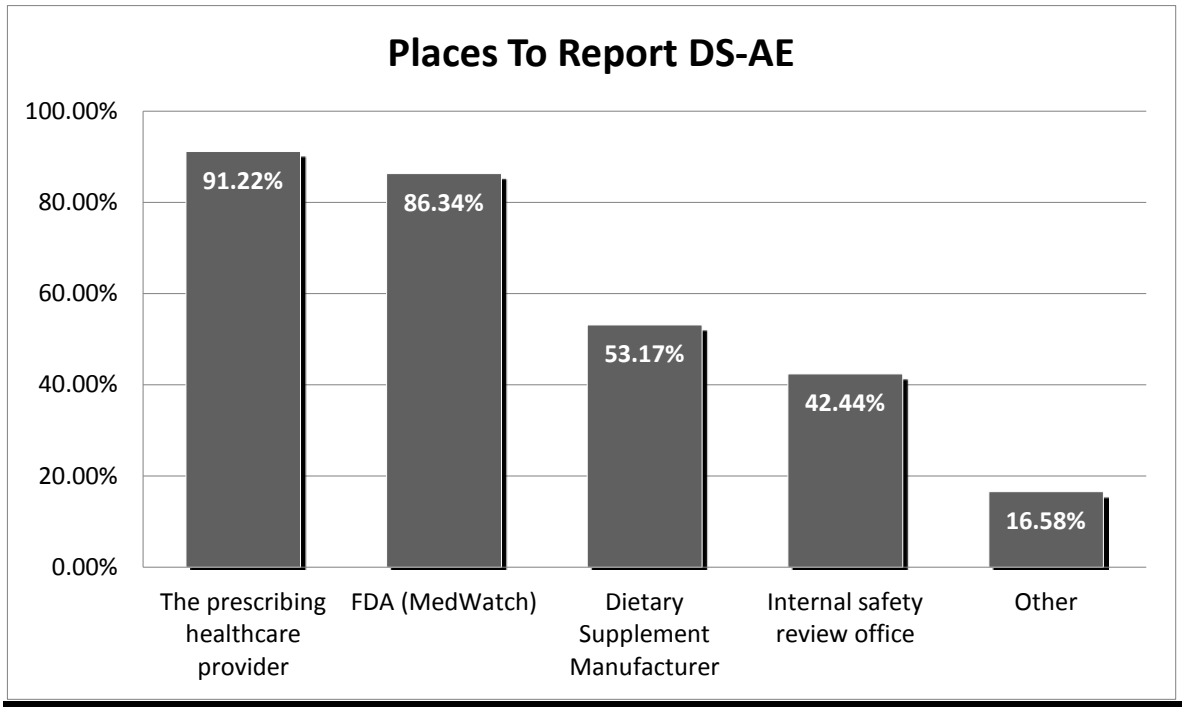


Figure 4.4 – Percentage distribution of participant opinion on places to report a DS-AE

Table 4.11 – Places to report a DS adverse event by practice setting

	Practice Setting (%)			
Places to report	**Healthcare system**	**Community**	**Other**	**p-value**
The prescribing healthcare provider (n=187)	51.30%	26.70%	21.90%	0.787
Internal safety review office (n= 87)	70.10%	12.60%	17.20%	< 0.001
FDA (MedWatch) (n=177)	52.50%	23.70%	23.70%	0.008
DS Manufacturer (n=109)	48.00%	27.00%	25.00%	0.417

DS: dietary supplement; FDA: food and drug administration

Conjoint Analysis

Two models were run for each reporting place. Model-1 examined only the profile attributes (patient's age, initiation of DS, time since last change of drug therapy, evidence supporting the AE, and outcome of the AE). Model-2 examined the impact of other characteristics and all two-way interactions of the attributes on the pharmacist's decision to report the AE. The average part-worth utility of each attribute level and the relative importance of each attribute were estimated for each reporting place: prescriber (model1-1), drug manufacturer (model1-2), DS manufacturer (model1-3), and FDA (model1-4). Note that part-worths are the coefficients of random-effect linear regression models using the ordinary least square (OLS) method. They are relative measures and sum to zero for each attribute. In model-2, all two-way interaction terms between the five attributes were included, as explained earlier in the methods section. In addition, covariates from other characteristics were included as well. These interaction terms, covariates and other variables were retained only if they were significant at α-level of 0.05 in a separate backward stepwise selection regression model for each reporting place. The detailed results of these models are presented in Appendix F.

Reporting to the Prescriber (Model 1)

Table 4.12 presents the average utility information of each attribute level that participants used to make their decision to report the AE to the prescriber. No interaction terms or covariate of other participant characteristics were included in this model. The average part-worth utility with the 95% CI, standard error, and the significance level of each attribute level are listed.

There was no significant difference in the part-worth utility of each level of the age of patient attribute (level “25 years”, “45 years”, or “70 years”) and the mean utility of this attribute (zero). The mean utility of any attribute is zero because effect coding was used in this regression model and the sum of utilities must be zero. The utility range of this attribute was (0.10). For the Initiation of DS attribute, the part-worth utility for reporting to the prescriber if DS was initiated “within the past 2 weeks” is significantly higher than zero, 0.09 (95% CI= 0.00, 0.18) ($p = 0.043$) and less than zero if DS was initiated “about 6 months ago”. The utility range of this attribute was (0.19). For the time since last change of drug therapy attribute, the part-worth utility for reporting to the prescriber if drug therapy was last changed “within the past 2 weeks” is not significantly higher than zero and less than zero if DS was changed “about 6 months ago”. The utility range of this attribute was (0.16).

The part-worth utility for change of drug therapy “within the past 2 weeks” was not significantly different from 0. The evidence of the AE in the literature (utility range = 0.85) and the outcome of the AE had higher participants’ utility (utility range = 1.58) in making

the decision to report an AE than other attributes utilities, (Table 4.20). For the evidence of AE attribute, the average participants' utility for reporting to the prescriber was 0.69 (reference) if there was consistent evidence in the literature supporting the AE. On the other hand, if there was no evidence in the literature supporting the AE, the average participants' utility for reporting the AE to the prescriber is significantly less than zero at -0.78 (95% CI=-0.91, -0.65) ($p<0.001$), and it was not significantly different from zero if there was inconsistent (or mixed) evidence in the literature.

The average participants' utility for reporting to the prescriber was significantly more than zero, 0.54 (95% CI=0.37, 0.71) ($p<0.001$), if the AE resulted in permanent disability, significantly more than zero if the AE required hospitalization, 0.18 (95% CI=0.03, 0.34) ($p = 0.023$), and not significantly different from zero if it required outpatient or emergency room (ER) visit. On the other hand, if the outcome of the AE was self-limited, meaning that it resolved upon discontinuation of DS, the average participants' utility for reporting to the prescriber was -0.76 (reference).

As in figure 4.5 and Table 4.20, the most important attribute in reporting a DS related AE to the prescriber was the evidence supporting the AE (45.25%) followed by the outcome of the AE (39.58%). Initiation of DS, time since change of drug therapy and age of the patient were not as important.

Table 4.12 – Results of the conjoint analysis for reporting to the prescriber (model 1)

Attributes	Levels	General Model Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	-0.06 (Reference*)	—	—
	b. 45 years	-0.08 (-0.21, 0.05)	0.07	0.214
	c. 70 years	0.02 (-.11, 0.15)	0.07	0.753
2. Initiation of DS†	a. Within the past 2 weeks	0.09 (0.00, 0.18)	0.05	0.043
	b. About 6 months ago	-0.09 (Reference*)	—	—
3. Time since last change of drug therapy	a. Within the past 2 weeks	0.08 (-0.01, 0.17)	0.05	0.093
	b. About 6 months ago	-0.08 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.69 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.09 (-0.04, 0.22)	0.07	0.173
	c. No evidence in the literature	-0.78 (-0.91, -0.65)	0.07	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.74 (Reference*)	—	—
	b. Required outpatient/ER visit	0.02 (-0.14, 0.18)	0.08	0.786
	c. Required hospitalization	0.18 (0.03, 0.34)	0.08	0.023
	d. Resulted in permanent disability	0.54 (0.37, 0.71)	0.08	<0.001
Constant		4.44 (4.28, 4.61)	0.08	<0.001
Number of obs	811			
Number of groups	213			
Pseudo R^2	30.28%			
Chi Square	285.33			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

† The attribute is significantly different from zero at p = 0.05 level (Table 4.22)

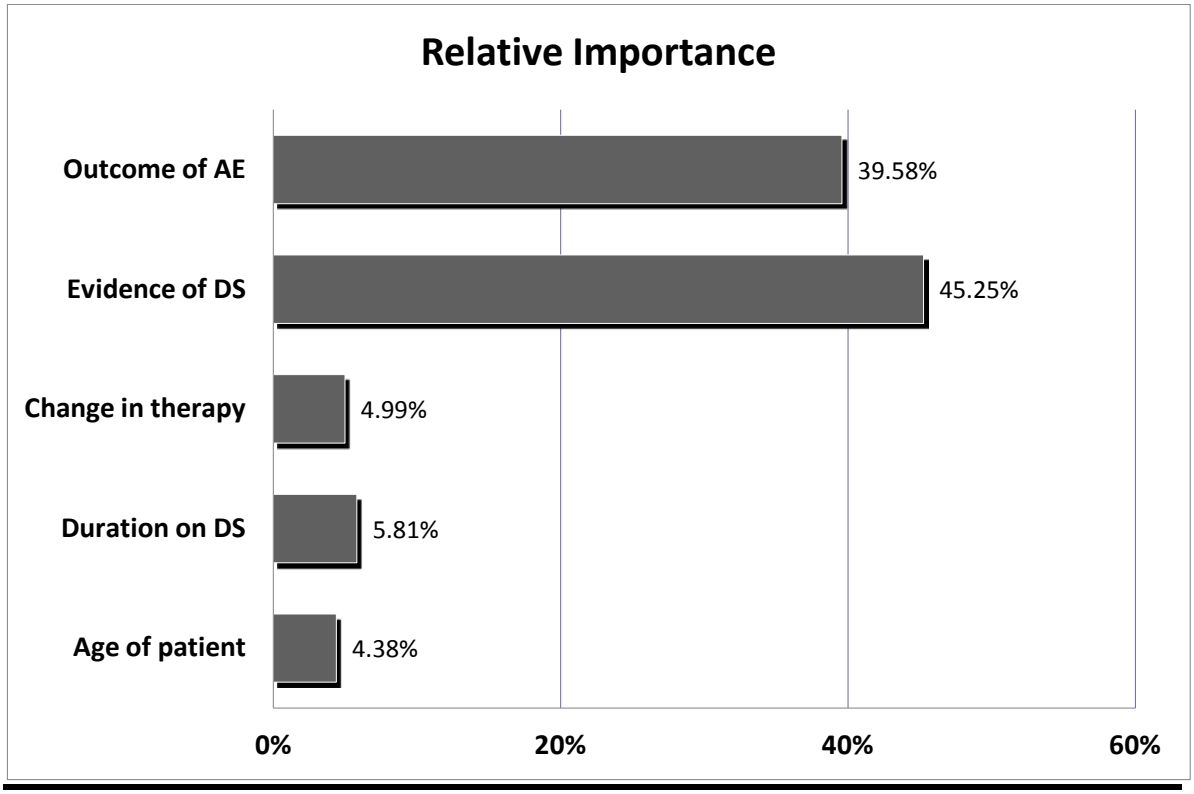


Figure 4.5 – Relative importance of attributes for reporting to the prescriber (model 1)
DS: dietary supplement; AE: adverse event

Reporting to the Prescriber (Model 2)

Table 4.15 presents the adjusted average part-worth utility of each attribute level that participants used to decide on reporting the AE to the prescriber. The significant interaction terms between attributes and the significant covariate of other participant's characteristics were included in the model. None of the interaction terms were retained in the backward selection model. The covariates that were retained in the backward selection model and in the adjusted model 2 were "encountered a patient with a suspected DS-AE", "*primary* practice setting in outpatient pharmacy", "overall attitude toward the safety of DS", "African American ethnicity", "no previous reporting of an AE to the FDA MedWatch system", "overall attitude toward the clinical use of DS", "the status of not completing residency or fellowship program", and "*primary* practice setting in ambulatory healthcare facility" (Appendix F).

After including the significant interaction terms and covariates, the initiation of DS within the past 2 weeks was no longer significant, 0.09 (95% CI= 0.00, 0.19) (p = 0.053). No other significance levels changed. The size of some part-worth utilities and the importance of the some attributes, however, resulted in some small changes after including the significant interaction terms and covariates. The part-worth utility of change in drug therapy in the past 2 weeks decreased from 0.08 to 0.05. The importance of outcome of the AE increased from 39.58% to 41.21% and the importance of time since last change in drug therapy decreased from 4.99% to 2.74%. The small changes in importance of other are also reported (Figure 4.6). The range of part-worth utilities changed as well after including the

significant interaction terms and covariates (Table 4.20 and Table 4.21). The “time since last change of drug therapy” attribute produced the largest change; from 0.16 to 0.09. The “age of patient” attribute resulted in a small increase and the other attributes resulted in small decrease.

Table 4.13 – Results of the conjoint analysis for reporting to the prescriber (model 2)

Attributes	Levels	General Model Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	0.07 (Reference*)	—	—
	b. 45 years	-0.10 (-0.23, 0.03)	0.07	0.137
	c. 70 years	0.03 (-.11, 0.16)	0.07	0.699
2. Initiation of DS	a. Within the past 2 weeks	0.09 (0.00, 0.19)	0.05	0.053
	b. About 6 months ago	-0.09 (Reference*)	—	—
3. Time since last change of drug therapy	a. Within the past 2 weeks	0.05 (-0.05, 0.14)	0.05	0.356
	b. About 6 months ago	-0.05 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.69 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.12 (-0.01, 0.26)	0.07	0.079
	c. No evidence in the literature	-0.82 (-0.95, -0.68)	0.07	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.79 (Reference*)	—	—
	b. Required outpatient/ER visit	0.03 (-0.13, 0.20)	0.08	0.701
	c. Required hospitalization	0.21 (0.05, 0.37)	0.08	0.011
	d. Resulted in permanent disability	0.57 (0.39, 0.74)	0.09	<0.001
Constant		4.75 (4.06, 5.45)	0.35	<0.001
Number of obs	754			
Number of groups	196			
Pseudo R^2	32.89%			
Chi Square	322.51			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

**No significant interaction terms were retained at p = 0.05 level

† The attribute is significantly different from zero at p = 0.05 level (Table 4.23)

Note: see appendix F for complete results with the covariates that were retained in this model

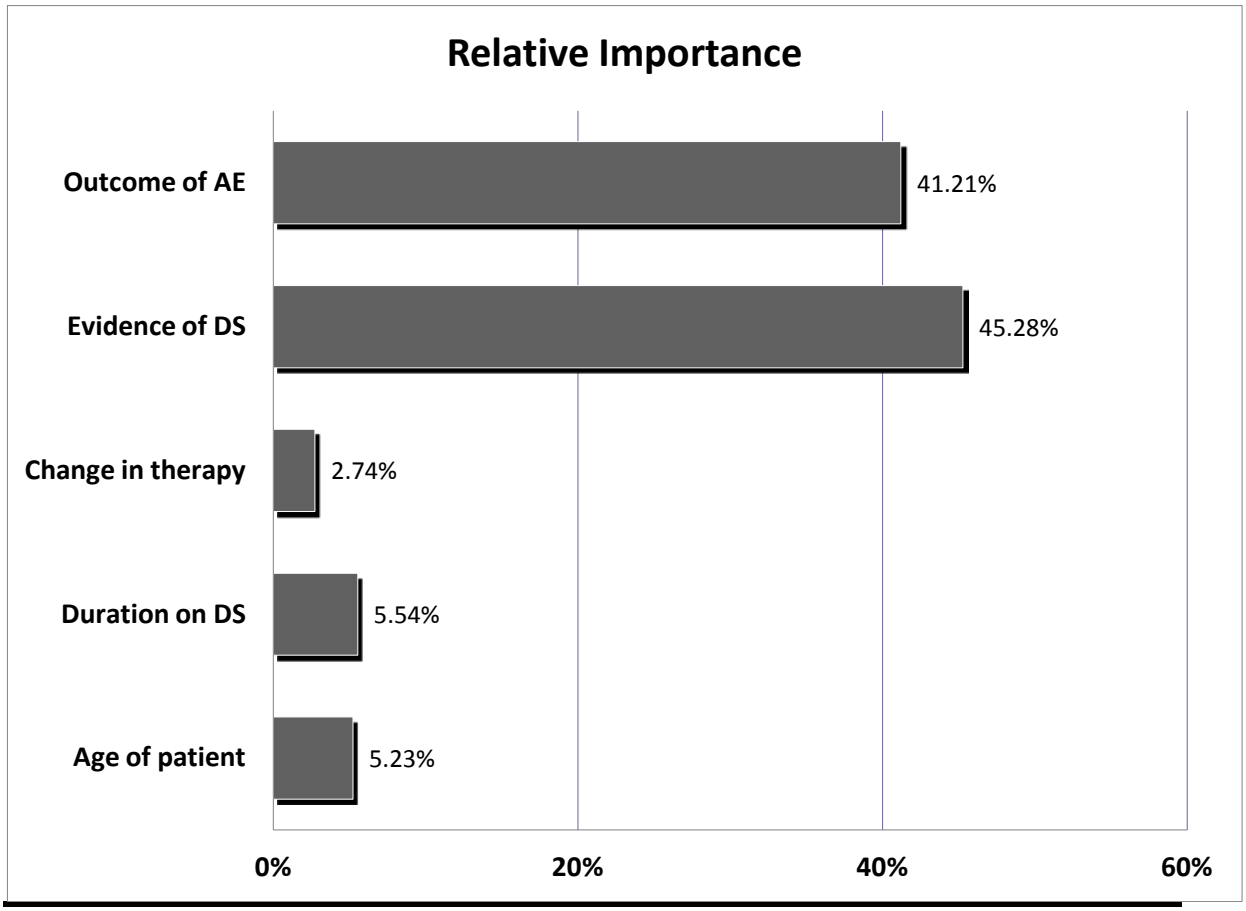


Figure 4.6 – Relative importance of attributes for reporting to the prescriber (model 2)
DS: dietary supplement; AE: adverse event

Reporting to the Drug Manufacturer (Model 1)

Table 4.14 presents the average utility information of each attribute level that participants used to make their decision to report the AE to the drug manufacturer. No interaction terms or covariate of other participant characteristics were included in this model. The average part-worth utility with the 95% CI, standard error, and the significance level of each attribute level are listed.

There was no significant difference in the part-worth utility of each level of the age of patient attribute (level "25 years", "45 years", or "70 years") and the mean utility of this attribute (zero). The utility range of this attribute was (0.11). For the initiation of DS attribute, the part-worth utility for reporting to the drug manufacturer if DS was initiated "within the past 2 weeks" is significantly higher than zero, 0.14 (95% CI= 0.05, 0.22) (p = 0.002) and non-significantly lower than zero if DS was initiated "about 6 months ago". The utility range of this attribute was (0.27). For the time since last change of drug therapy attribute, the part-worth utility for reporting to the prescriber if drug therapy was last changed "within the past 2 weeks" is not significantly higher than zero and less than zero if DS was changed "about 6 months ago". The utility range of this attribute was (0.17).

Changing of drug therapy "within the past 2 weeks" had not significantly more part-worth utility and "about 6 months ago" had not significantly less part-worth utility than zero in reporting the AE to the drug manufacturer.

The evidence of the AE in the literature (utility range = 0.85) and the outcome of the AE had higher participants' utilities (utility range = 1.58) in making the decision to

report an AE than other attributes utilities, (Table 4.20). For the evidence of AE attribute, the average participants' utility for reporting to the drug manufacturer is 0.38 (reference) if there was consistent evidence in the literature supporting the AE. On the other hand, if there was no evidence in the literature supporting the AE, the average participants' utility for reporting the AE to the drug manufacturer was significantly less than zero at -0.47 (95% CI=-0.60, -0.35) ($p<0.001$) and it was not significantly different from zero if there was inconsistent (or mixed) evidence in the literature.

The average participants' utility for reporting to the drug manufacturer was significantly more than zero, 0.82 (95% CI=0.67, 0.98) ($p<0.001$), if the AE resulted in permanent disability, not significantly different from zero if the AE required hospitalization, and significantly less than zero, -0.15 (95% CI=-0.30, 0.00) ($p = 0.046$), if it required outpatient or ER visit. On the other hand, if the outcome of the AE was self-limited and resolved upon discontinuation of DS, the average participants' utility for reporting to the drug manufacturer was -0.76 (reference).

As in Figure 4.7, the most important attribute in reporting a DS related AE to the drug manufacturer were the outcome of the AE (53.55%) followed by the evidence supporting the AE (28.85%) and initiation of DS (9.15%). Time since change of drug therapy and age of the patient were not as important.

Table 4.14 – Results of the conjoint analysis for reporting to the drug manufacturer (model 1)

Attributes	Levels	General Model Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	0.01 (Reference*)	—	—
	b. 45 years	-0.06 (-0.18, 0.06)	0.06	0.319
	c. 70 years	0.05 (-.07, 0.17)	0.06	0.445
2. Initiation of DS†	a. Within the past 2 weeks	0.14 (0.05, 0.22)	0.04	0.002
	b. About 6 months ago	-0.14 (Reference*)	—	—
3. Time since last change of drug therapy	a. Within the past 2 weeks	0.09 (-0.01, 0.17)	0.05	0.057
	b. About 6 months ago	-0.09 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.38 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.09 (-0.03, 0.22)	0.06	0.147
	c. No evidence in the literature	-0.47 (-0.60, -0.35)	0.06	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.76 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.15 (-0.30, 0.00)	0.08	0.046
	c. Required hospitalization	0.09 (-0.06, 0.24)	0.08	0.238
	d. Resulted in permanent disability	0.82 (0.67, 0.98)	0.08	<0.001
Constant		3.06 (2.88, 3.25)	0.09	<0.001
Number of obs	811			
Number of groups	213			
Pseudo R^2	26.67%			
Chi Square	239.69			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

† The attribute is significantly different from zero at p = 0.05 level (Table 4.22)

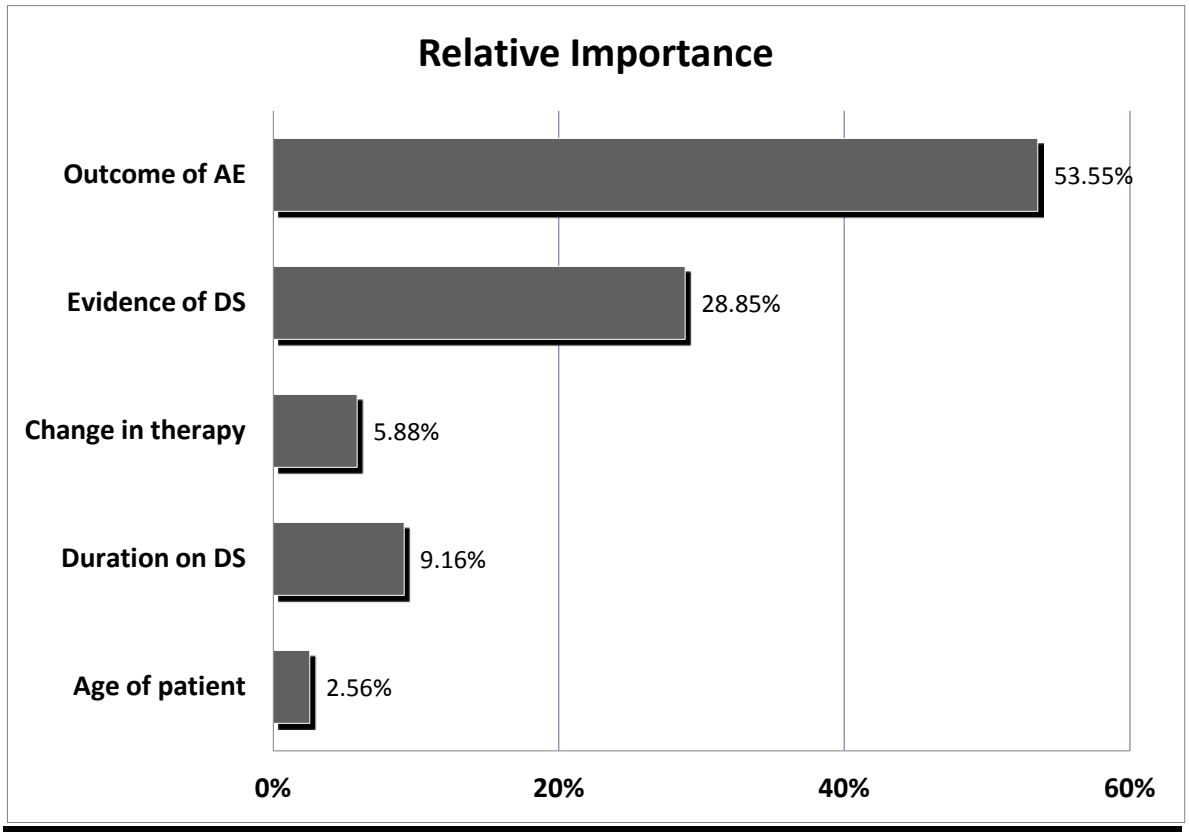


Figure 4.7 – Relative importance of attributes for reporting to the drug manufacturer (model 1)
DS: dietary supplement; AE: adverse event

Reporting to the Drug Manufacturer (Model 2)

Table 4.15 presents the adjusted average part-worth utility of each attribute level that participants used to decide on reporting the AE to the drug manufacturer. The significant interaction terms between attributes and the significant covariate of other participant's characteristics were included in the model. None of the interaction terms were retained in a backward selection model of all attributes, interactions and covariates. The covariates that were retained in the backward selection model and were included in the adjusted model 2 are "primary practice setting in community pharmacy", "overall attitude toward the clinical use of DS", "did not encounter a patient with a suspected DS-AE", "previous reporting of an AE to the FDA MedWatch system without including a DS in the report", "overall attitude toward the safety of DS", "primary practice setting in ambulatory academia", "other races", "primary practice setting in ambulatory healthcare facility", "African American ethnicity", "no previous reporting of an AE to the drug manufacturer", and "previous reporting of an AE to the DS manufacturer" (Appendix F).

After including the significant interaction terms and covariates, the significance levels of the attributes did not change. The size of some part-worth utilities and the importance of the some attributes, however, resulted in some small change after including the significant interaction terms and covariates (Table 14 and Table 15). The importance of other attributes produced small changes. The largest change was in the "age of patient"; increasing from 2.56% to 4.04% (Figure 4.6). The range of part-worth utilities changed as well after including the significant interaction terms and covariates (Table 4.20 and Table

4.21). The “time since last change of drug therapy” attribute resulted in a small decrease and the other attributes resulted in a small increase.

Table 4.15 – Results of the conjoint analysis for reporting to the drug manufacturer (model 2)

Attributes	Levels	General Model Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	0.03 (Reference*)	—	—
	b. 45 years	-0.08 (-0.20, 0.05)	0.06	0.223
	c. 70 years	0.05 (-.08, 0.18)	0.07	0.474
2. Initiation of DS†	a. Within the past 2 weeks	0.15 (0.06, 0.24)	0.05	0.001
	b. About 6 months ago	-0.15 (Reference*)	—	—
3. Time since last change of drug therapy	a. Within the past 2 weeks	0.08 (-0.02, 0.17)	0.05	0.106
	b. About 6 months ago	-0.08 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.40 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.11 (-0.02, 0.25)	0.07	0.085
	c. No evidence in the literature	-0.51 (-0.64, -0.39)	0.06	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.77 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.17 (-0.33, -0.02)	0.08	0.029
	c. Required hospitalization	0.10 (-0.06, 0.25)	0.08	0.218
	d. Resulted in permanent disability	0.85 (0.68, 1.01)	0.08	<0.001
Constant		5.49 (3.37, 7.26)	0.90	<0.001
Number of obs	758			
Number of groups	197			
Pseudo R^2	28.30%			
Chi Square	288.10			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

† The attribute is significantly different from zero at p = 0.05 level (Table 4.23)

Note: see appendix F for complete results with the interaction terms and the covariates that were retained in this model

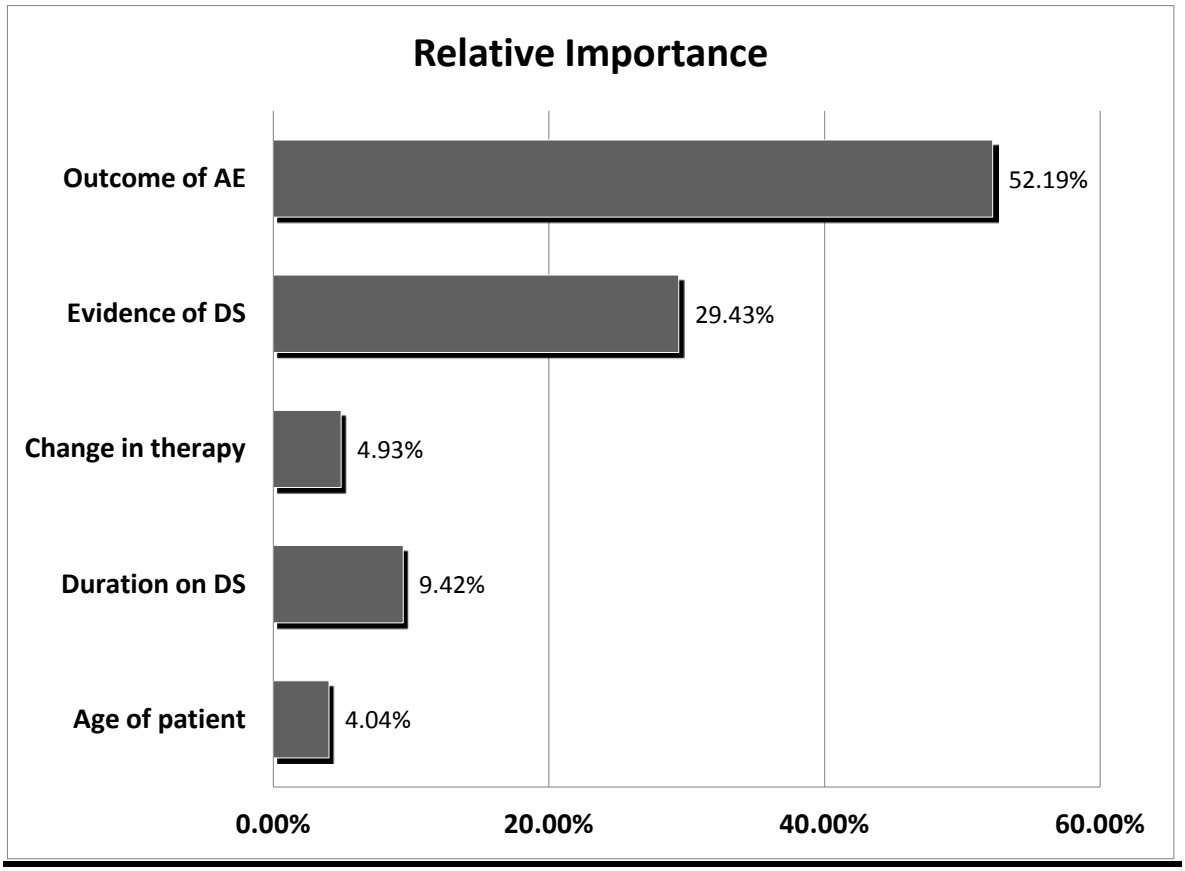


Figure 4.8 – Relative importance of attributes for reporting to the drug manufacturer (model 2)
DS: dietary supplement; AE: adverse event

Reporting to the Dietary Supplement Manufacturer (Model 1)

Table 4.16 presents the average utility information of each attribute level that participants used to make their decision to report the AE to the DS manufacturer. No interaction terms or covariate of other participant's characteristics were included in this model. The average part-worth utility with the 95% CI, standard error, and the significance level of each attribute level are listed.

There was no significant difference in the part-worth utility of each level of the age of patient attribute (level "25 years", "45 years", or "70 years") and the mean utility of this attribute (zero). The utility range of this attribute was (0.17). Initiation of DS "within the past 2 weeks" had not significantly more part-worth utility and "about 6 months ago" had not significantly less part-worth utility than zero in reporting the AE to the DS manufacturer. The utility range of this attribute was (0.09). For the time since last change of drug therapy attribute, the part-worth utility for reporting to the prescriber if drug therapy was last changed "within the past 2 weeks" is not significantly higher than zero and less than zero if DS was changed "about 6 months ago". The utility range of this attribute was (0.20).

For the changing of drug therapy attribute, the part-worth utility for reporting to the DS manufacturer was significantly higher than zero, 0.10 (95% CI= 0.01, 0.18) ($p = 0.026$) if drug therapy was changed "within the past 2 weeks" and was not significantly less than zero if drug therapy was initiated "about 6 months ago".

The evidence of the AE in the literature (utility range = 0.81) and the outcome of the AE resulted in higher participants' utilities (utility range = 1.43) in making the decision to report an AE than other attributes utilities, (Table 4.20). For the evidence of AE attribute, the average participants' utility for reporting the AE to the DS manufacturer was 0.41 (reference) if there was consistent evidence in the literature supporting the AE. On the other hand, if there was no evidence in the literature supporting the AE, the average participants' utility for reporting the AE to the DS manufacturer was significantly less than zero at -0.41 (95% CI=-0.52, -0.29) ($p<0.001$) and it was not significantly different from zero if there was inconsistent (or mixed) evidence in the literature.

The average participants' utility for reporting to the DS manufacturer was significantly more than zero, 0.79 (95% CI=0.64, 0.95) ($p<0.001$), if the AE resulted in permanent disability, not significantly different from zero if the AE required hospitalization and significantly less than zero if it required outpatient or ER visit, -0.20 (95% CI=-0.35, -0.06) ($p = 0.006$). On the other hand, if the outcome of the AE was self-limited and resolved upon discontinuation of DS, the average participants' utility for reporting to the DS manufacturer was -1.03 (reference).

As in figure 4.9 and Table 4.20, the most important attribute in reporting a DS related AE to the DS manufacturer were the outcome of the AE (49.57%) followed by the evidence supporting the AE (33.91%). Initiation of DS, time since change of drug therapy and age of the patient were not as important.

Table 4.16 – Results of the conjoint analysis for reporting to the dietary supplement manufacturer (model 1)

Attributes	Levels	General Model Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	-0.02 (Reference*)	—	—
	b. 45 years	-0.07 (-0.19, 0.04)	0.06	0.210
	c. 70 years	0.09 (-.03, 0.21)	0.06	0.130
2. Initiation of DS	a. Within the past 2 weeks	0.05 (-0.04, 0.13)	0.04	0.265
	b. About 6 months ago	-0.05 (Reference*)	—	—
3. Time since last change of drug therapy†	a. Within the past 2 weeks	0.10 (0.01, 0.18)	0.04	0.026
	b. About 6 months ago	-0.10 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.41 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.00 (-0.12, 0.12)	0.06	0.971
	c. No evidence in the literature	-0.41 (-0.52, -0.29)	0.06	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-1.03 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.20 (-0.35, -0.06)	0.07	0.006
	c. Required hospitalization	0.04 (-0.10, 0.18)	0.07	0.557
	d. Resulted in permanent disability	0.79 (0.64, 0.95)	0.08	<0.001
Constant		2.85 (2.67, 3.03)	0.09	<0.001
Number of obs	811			
Number of groups	213			
Pseudo R^2	24.61%			
Chi Square	215.78			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

† The attribute is significantly different from zero at p = 0.05 level (Table 4.22)

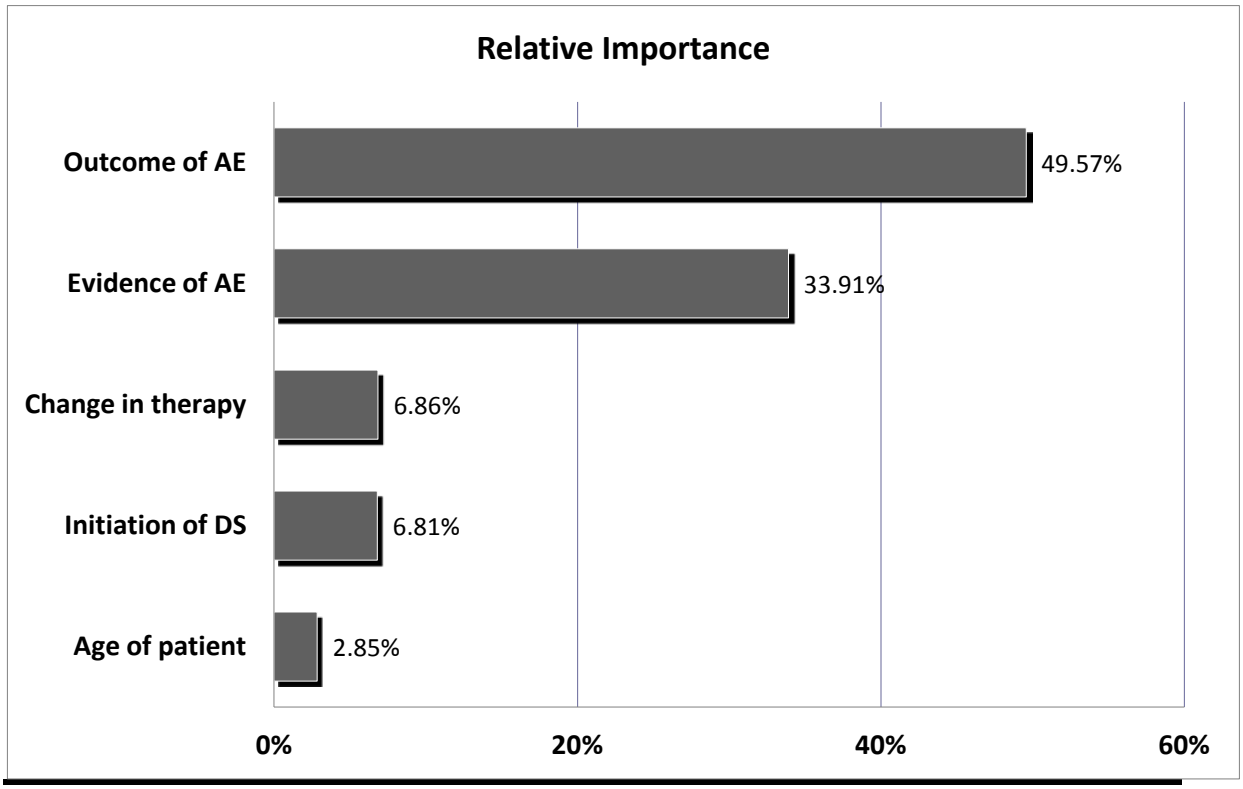


Figure 4.9 – Relative importance of attributes for reporting to the dietary supplement manufacturer (model 1)
DS: dietary supplement; AE: adverse event

Reporting to the Dietary Supplement Manufacturer (Model 2)

Table 4.17 presents the adjusted average part-worth utility of each attribute level that participants used to decide on reporting the AE to the DS manufacturer. The significant interaction terms between attributes and the significant covariate of other participant characteristics were included in the model. None of the interaction terms were retained in a backward selection model of all attributes, interactions and covariates. The covariates that were retained in the backward selection model and were included in the adjusted model-2 were "no previous reporting of an AE to the drug manufacturer", "*primary* practice setting in ambulatory healthcare facility", "no previous reporting of an AE to the DS manufacturer", "African American ethnicity", "female gender", "the status of not completing either residency or fellowship program", "did not encounter a patient with a suspected DS-AE", and "no previous reporting of an AE to the drug manufacturer"**;** (Appendix F).

After including the significant interaction terms and covariates, the significance levels of the attributes did not change. The size of some part-worth utilities and the importance of the some attributes, however, resulted in some small changes after including the significant interaction terms and covariates (Table 16 and Table 17). The importance of other attributes also resulted in some changes. The "evidence of AE" decreased from 33.91% to 29.85%, the "initiation of DS" decreased form 6.81% to 3.92%, and the "age of patient" increased from 2.85% to 6.79% (Figure 4.9 and Figure 4.10). The range of part-worth utilities changed as well after including the significant interaction terms and

covariates (Table 4.20 and Table 4.21). The “time since last change of drug therapy” attribute resulted in a small decrease and the other attributes resulted in small increases. The largest changes were in “age of patient” that increased from 0.17 to 0.19 and “initiation of DS” that increased from 0.09 to 0.11.

Table 4.17 – Results of the conjoint analysis for reporting to the dietary supplement manufacturer (model 2)

Attributes	Levels	General Model		
		Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	-0.01 (Reference*)	—	—
	b. 45 years	-0.09 (-0.22, 0.03)	0.06	0.132
	c. 70 years	0.10 (-0.03, 0.22)	0.06	0.125
2. Initiation of DS	a. Within the past 2 weeks	0.06 (-0.03, 0.14)	0.04	0.212
	b. About 6 months ago	-0.06 (Reference*)	—	—
3. Time since last change of drug therapy†	a. Within the past 2 weeks	0.10 (0.01, 0.19)	0.05	0.035
	b. About 6 months ago	-0.10 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.41 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.02 (-0.10, 0.15)	0.06	0.730
	c. No evidence in the literature	-0.43 (-0.56, -0.31)	0.06	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-1.09 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.21 (-0.36, -0.05)	0.08	0.008
	c. Required hospitalization	0.04 (-0.11, 0.19)	0.08	0.598
	d. Resulted in permanent disability	0.82 (0.66, 0.98)	0.08	<0.001
Constant		4.99 (3.36, 6.61)	0.83	<0.001
Number of obs	746			
Number of groups	194			
Pseudo R^2	26.04%			
Chi Square	245.51			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

**No significant interaction terms were retained at p = 0.05 level

† The attribute is significantly different from zero at p = 0.05 level (Table 4.23)

Note: see appendix F for complete results with the covariates that were retained in this model

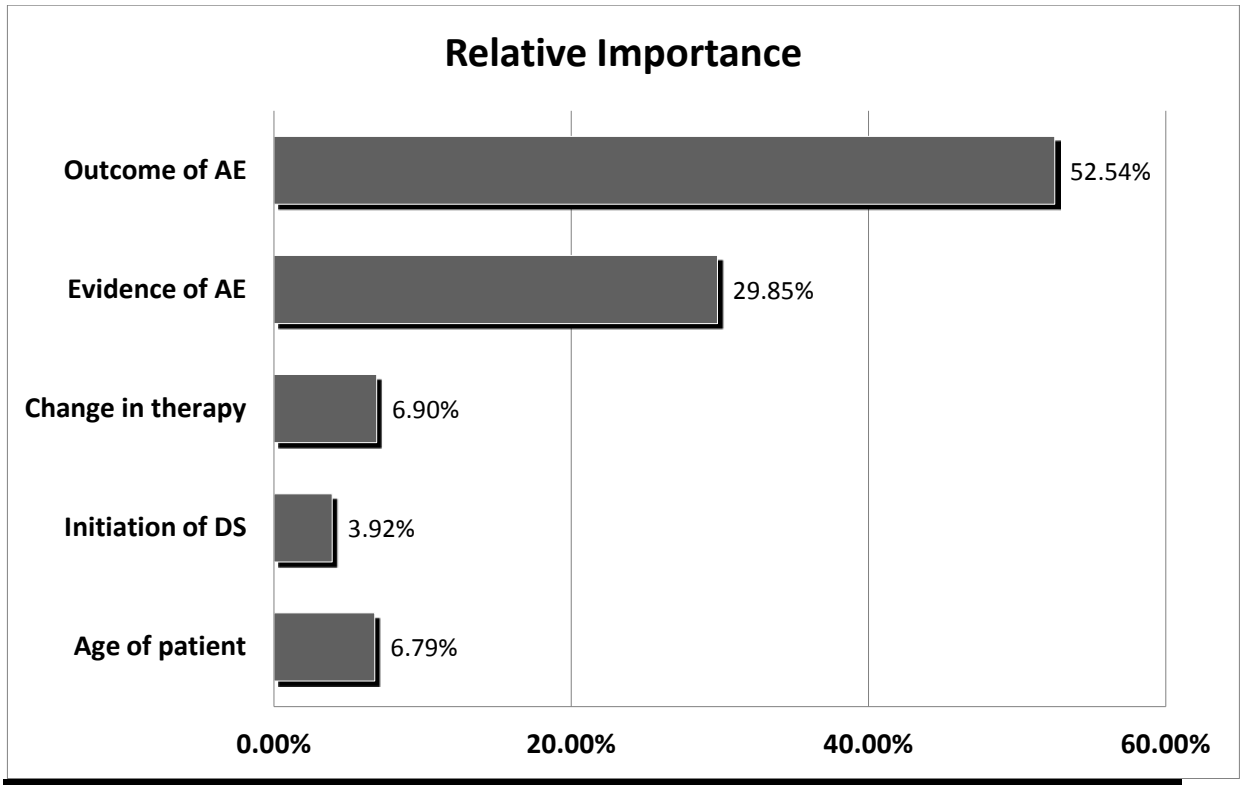


Figure 4.10 – Relative importance of attributes for reporting to the dietary supplement manufacturer (model 2)
DS: dietary supplement; AE: adverse event

Reporting to the FDA (Model 1)

Table 4.18 presents the average utility information of each attribute level that participants used to make their decision to report the AE to FDA. No interaction terms or covariate of other participant characteristics were included in this model. The average part-worth utility with the 95% CI, standard error, and the significance level of each attribute level are listed.

There was no significant difference in the part-worth utility of each level of the age of patient attribute (level "25 years", "45 years", or "70 years") and the mean utility of this attribute (zero). The utility range of this attribute was (0.10). Initiation of DS "within the past 2 weeks" had significantly more part-worth utility than zero, 0.11 (95% CI= 0.03, 0.20) (p = 0.011) and "about 6 months ago" had less part-worth utility than zero in reporting the AE to FDA. The utility range of this attribute was (0.23).

For the changing of drug therapy attribute, the part-worth utility for reporting to the FDA MedWatch system was significantly more than zero, 0.12 (95% CI= 0.02, 0.21) (p = 0.013) if drug therapy was changed "within the past 2 weeks" and was less than zero if drug therapy was initiated "about 6 months ago". The utility range of this attribute was (0.23).

The evidence of the AE in the literature (utility range = 1.14) and the outcome of the AE resulted in higher participants' utility (utility range = 1.67) in making the decision to report an AE than other attributes utilities, (Table 4.20). For the evidence of AE attribute, the average participants' utility for reporting the AE to FDA was 0.54 (reference)

if there was consistent evidence in the literature supporting the AE. On the other hand, if there was no evidence in the literature supporting the AE, the average participants' utility for reporting the AE to FDA was significantly less than zero -0.60 (95% CI=-0.72, -0.47) ($p<0.001$) and it was not significantly different from zero if there was inconsistent (or mixed) evidence in the literature.

The average participants' utility for reporting to the FDA MedWatch system was significantly more than zero, 0.84 (95% CI=0.67, 1.00) ($p<0.001$), if the AE resulted in permanent disability, significantly more than zero if the AE required hospitalization 0.19 (95% CI=0.04, 0.34) ($p = 0.015$), and significantly less than zero if it required an outpatient or ER visit, -0.19 (95% CI=-0.34, -0.04) ($p = 0.016$). On the other hand, if the outcome of the AE was self-limited and resolved upon discontinuation of DS, the average participants' utility for reporting to FDA was -0.83 (reference).

As in figure 4.11 and Table 4.20, the most important attribute in reporting a DS related AE to FDA were the outcome of the AE (49.57%) followed by the evidence supporting the AE (33.91%). Initiation of DS, time since change of drug therapy and age of the patient were not as important.

Table 4.18 – Results of the conjoint analysis for reporting to the FDA (model 1)

Attributes	Levels	General Model: Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	0.02 (Reference*)	—	—
	b. 45 years	-0.06 (-0.18, 0.06)	0.06	0.345
	c. 70 years	0.04 (-.09, 0.61)	0.06	0.572
2. Initiation of DS†	a. Within the past 2 weeks	0.11 (0.03, 0.20)	0.04	0.011
	b. About 6 months ago	-0.11 (Reference*)	—	—
3. Time since last change of drug therapy†	a. Within the past 2 weeks	0.12 (0.02, 0.21)	0.05	0.013
	b. About 6 months ago	-0.12 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.54 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.06 (-0.07, 0.18)	0.07	0.399
	c. No evidence in the literature	-0.60 (-0.72, -0.47)	0.06	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.83 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.19 (-0.34, -0.04)	0.08	0.016
	c. Required hospitalization	0.19 (0.04, 0.34)	0.08	0.015
	d. Resulted in permanent disability	0.84 (0.67, 1.00)	0.08	<0.001
Constant		3.31 (3.12, 3.50)	0.10	<0.001
Number of obs	811			
Number of groups	213			
Pseudo R^2	31.92%			
Chi Square	304.58			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

† The attribute is significantly different from zero at p = 0.05 level (Table 4.22)

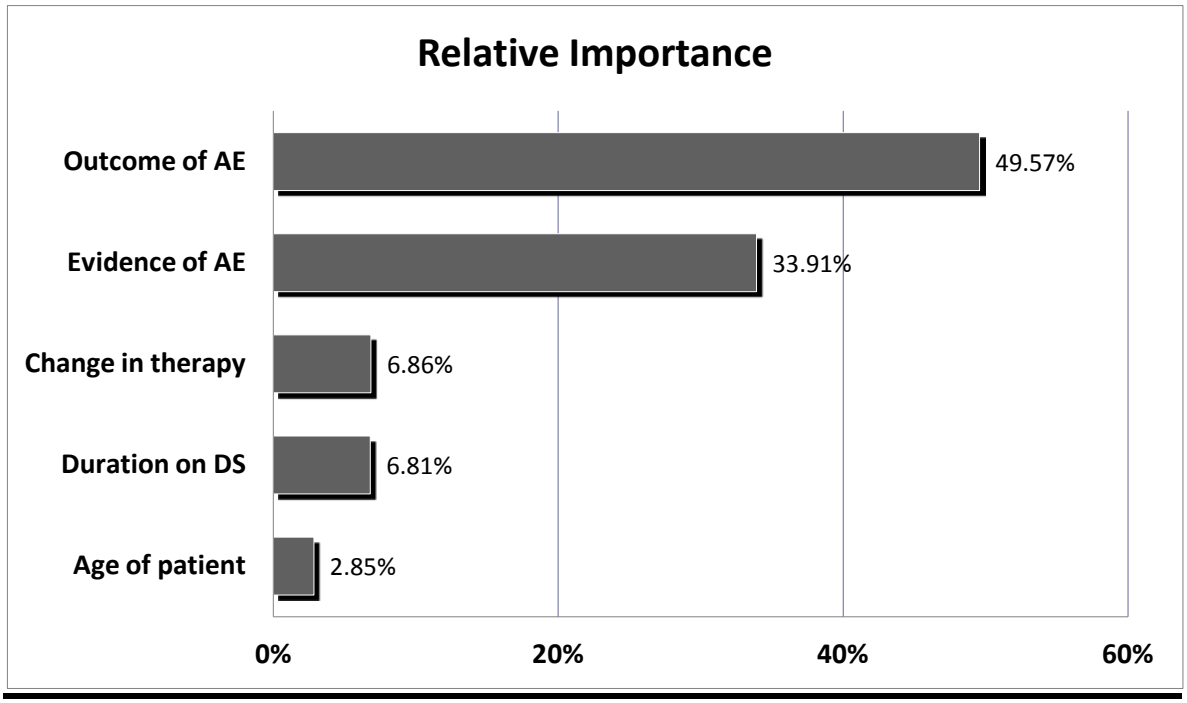


Figure 4.11 – Relative importance of attributes for reporting to the FDA MedWatch system (model 1)
DS: dietary supplement; AE: adverse event; FDA: food and drug administration

Reporting to the FDA (Model 2)

Table 4.19 presents the adjusted average part-worth utility of each attribute level that participants used to decide on reporting the AE to the FDA MedWatch system. The significant interaction terms between attributes and the significant covariate of other participant's characteristics were included in the model. The only interaction terms retained in a backward selection model that included all attributes, interactions and covariates was between "45 years age of patient" and "initiation of DS in the past two weeks". The covariates that were retained in the backward selection model and were included in the adjusted model-2 included "participant's age category of 50-59 years", "African American ethnicity", "previous reporting of an AE to the drug manufacturer with including a DS in the report", "*primary* practice setting in academia", "overall attitude toward the safety of DS", "overall attitude toward the clinical use of DS", "other races", "female gender", "participant's age category of 60 years or older", "primary practice setting in community pharmacy", "participant's age category of 30-39 years", "participant's age category of 40-49 years", "did not encounter a patient with a suspected DS-AE", "no previous reporting of an AE to the DS manufacturer", "primary practice setting in ambulatory healthcare facility", and "previous reporting of an AE to the FDA MedWatch system without including a DS in the report"**;** (Appendix F).

After including the significant interaction terms and covariates, the significance levels the attributes did not change. The size of some part-worth utilities and the importance of the some attributes, however, resulted in some small changes after including

the significant interaction terms and covariates (Table 18 and Table 19). The importance of other attributes resulted in small changes (Figure 4.11 and Figure 4.12). The ranges of part-worth utilities resulted in small changes as well after including the significant interaction terms and covariates (Table 4.20 and Table 4.21). Overall, there was a minimal modification on this model after including the significant interaction terms and covariates.

Table 4.19 – Results of the conjoint analysis for reporting to the FDA MedWatch system (model 2)

Attributes	Levels	General Model		
		Part Worth β (95% CI)	SE	p-value
1. Age of patient	a. 25 years	0.04 (Reference*)	—	—
	b. 45 years	-0.07 (-0.20, 0.06)	0.07	0.303
	c. 70 years	0.03 (-0.10, 0.16)	0.07	0.637
2. Initiation of DS†	a. Within the past 2 weeks	0.13 (-0.04, 0.22)	0.05	0.006
	b. About 6 months ago	-0.13 (Reference*)	—	—
3. Time since last change of drug therapy†	a. Within the past 2 weeks	0.10 (0.00, 0.20)	0.05	0.042
	b. About 6 months ago	-0.10 (Reference*)	—	—
4. Evidence of DS-AE†	a. Consistent evidence in the literature	0.55 (Reference*)	—	—
	b. Inconsistent (or mixed) evidence	0.09 (-0.05, 0.22)	0.07	0.211
	c. No evidence in the literature	-0.64 (-0.77, -0.51)	0.07	<0.001
5. Outcome of the DS-AE†	a. Self-limiting	-0.88 (Reference*)	—	—
	b. Required outpatient/ER visit	-0.18 (-0.34, -0.02)	0.08	0.026
	c. Required hospitalization	0.20 (0.04, 0.35)	0.08	0.014
	d. Resulted in permanent disability	0.83 (0.66, 1.00)	0.09	<0.001
Constant		3.55 (2.54, 4.56)	0.51	<0.001
Number of obs	750			
Number of groups	195			
Pseudo R^2	33.60%			
Chi Square	358.40			
p-value	<0.0001			

DS: dietary supplement; AE: adverse event; CI: confidence interval; ER: emergency room; SE: standard error

*This was calculated from the model using effects coding

**No significant interaction terms were retained at p = 0.05 level

† The attribute is significantly different from zero at p = 0.05 level (Table 4.23)

Note: see appendix F for complete results with the covariates that were retained in this model

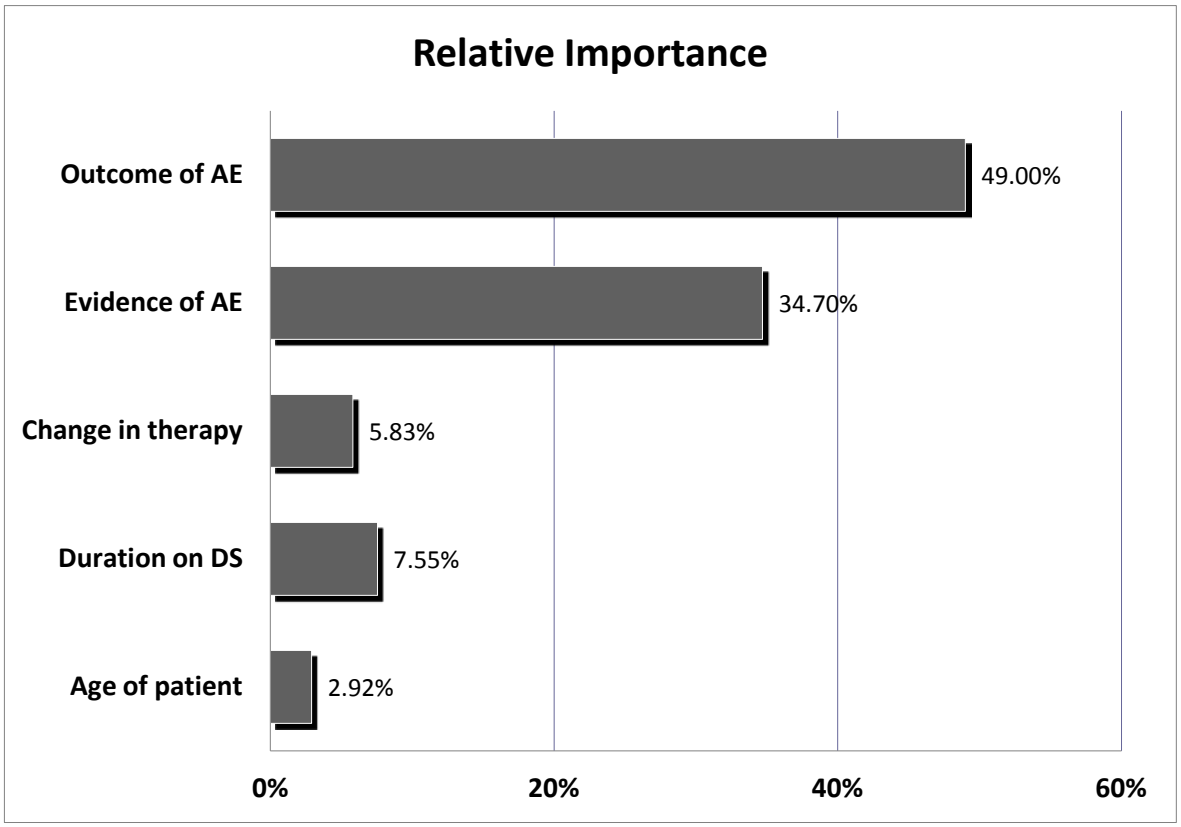


Figure 4.12 – Relative importance of attributes for reporting to the FDA MedWatch system (model 2)

Table 4.20 – Utility ranges of attributes for reporting to prescriber, drug manufacturer, dietary supplement manufacturer, and FDA MedWatch system (model 1)

Attributes	Utility Range			
	Prescriber	Drug manufacturer	DS manufacturer	FDA MedWatch system
1. Age of patient	0.10	0.11	0.17	0.10
2. Initiation of DS	0.19	0.27	0.09	0.23
3. Time since last change of drug therapy	0.16	0.17	0.20	0.23
4. Evidence of DS-AE	1.46	0.85	0.81	1.14
5. Outcome of the DS-AE	1.28	1.58	1.43	1.67

DS: dietary supplement; AE: adverse event; FDA: food and drug administration

Table 4.21 – Utility ranges of attributes for reporting to prescriber, drug manufacturer, dietary supplement manufacturer, and FDA MedWatch system (model 2)

Attributes	Utility Range			
	Prescriber	Drug manufacturer	DS manufacturer	FDA MedWatch system
1. Age of patient	0.13	0.13	0.19	0.10
2. Initiation of DS	0.18	0.29	0.11	0.26
3. Time since last change of drug therapy	0.09	0.15	0.19	0.20
4. Evidence of DS-AE	1.51	0.91	0.84	1.19
5. Outcome of the DS-AE	1.37	1.62	1.48	1.67

DS: dietary supplement; AE: adverse event; FDA: food and drug administration

Table 4.22 – Level of significance of attributes for reporting to prescriber, drug manufacturer, dietary supplement manufacturer, and FDA MedWatch system (model 1)

Attributes	Utility Range Chi^2 (p-value)			
	Prescriber	**Drug manufacturer**	**DS manufacturer**	**FDA MedWatch system**
6. Age of patient	1.67 (0.4344)	1.09 (0.5803)	2.62 (0.2694)	0.90 (0.6364)
7. Initiation of DS	4.09 (0.0430)	9.44 (0.0021)	1.24 (0.2648)	6.50 (0.0108)
8. Time since last change of drug therapy	2.82 (0.0929)	3.63 (0.0567)	4.95 (0.0261)	6.14 (0.0132)
9. Evidence of DS-AE	168.52 (<0.000)	65.34 (<0.000)	61.33 (<0.000)	108.80 (<0.000)
10. Outcome of the DS-AE	98.25 (<0.000)	153.82 (<0.000)	136.68 (<0.000)	169.97 (<0.000)

DS: dietary supplement; AE: adverse event; FDA: food and drug administration

Table 4.23 – Level of significance of attributes for reporting to prescriber, drug manufacturer, dietary supplement manufacturer, and FDA MedWatch system (model 2)

Attributes	Utility Range			
	Prescriber	Drug manufacturer	DS manufacturer	FDA MedWatch system
6. Age of patient	2.39 (0.3032)	1.50 (0.4735)	3.07 (0.2150)	1.06 (0.5872)
7. Initiation of DS	3.75 (0.0528)	10.28 (0.0013)	1.56 (0.2116)	7.60 (0.0058)
8. Time since last change of drug therapy	0.85 (0.3559)	2.61 (0.1061)	4.46 (0.0348)	4.12 (0.0423)
9. Evidence of DS-AE	170.08 (<0.000)	70.10 (<0.000)	60.09 (<0.000)	108.62 (<0.000)
10. Outcome of the DS-AE	107.45 (<0.000)	150.46 (<0.000)	133.84 (<0.000)	157.58 (<0.000)

DS: dietary supplement; AE: adverse event; FDA: food and drug administration

Validation

The holdout validation method did not yield good results. In this method, the average predicted responses for the holdout profile were obtained using each of the final regression models that were developed using the five attributes, the significant interaction terms and covariates. The average difference between the observed responses for the holdout profile and the predicted responses was examined for each profile. The average difference was not significantly different from zero (4.31- 4.25=0.06; p = 0.2287) for the reporting to the prescriber (Model 2). The average difference was not significantly different from zero (2.98- 2.93=0.06; p = 0.2621) for the reporting to drug manufacturer (Model 2). The average difference was significantly different from zero (2.73- 2.91= -0.18; p = 0.0004) for the reporting to DS manufacturer (Model 2). The average difference was significantly different from zero (3.22- 4.25= -1.02; p = < 0.000) for the reporting to FDA (Model 2). The models were not good in predicting reporting responses to DS manufacturer and FDA. However, prediction of responses was not the general purpose of this study. The purpose of this study was understating the importance of the five selected attributes on participating pharmacists' decision to report a DS-AE.

CHAPTER 5: DISCUSSION

This study attempted to describe practicing pharmacists' attitudes toward the safety and clinical use of DS, level of knowledge about DS and DS regulations and other characteristics including the usage, availability and usefulness of DS information resources. It also attempted to determine the importance of selected attributes that influence a pharmacist's decision to report a DS related AE to different agencies using a CA approach. Five attributes were used in the conjoint models; the effect of other characteristics was also considered.

Participant Characteristics

A total of 206 practicing pharmacists finished the questionnaire with complete responses. The response rate in this study was estimated to be 27% which may seem low but is relatively good for an online survey.[82] The response rate in a recent study by Claudia et al. using online surveys in a national sample of medical office managers and physicians to evaluate their preferences for seven vaccine presentation attributes using a CA approach was 13.5%.[81] Another national online survey study to determine institutional policies and practices related to the use of DS resulted in a response rate of 25%.[99] The response rate

was 27% in an online survey study to identify and evaluate commonly used drug information resources by pharmacists in Singapore.[83]

The majority of the participants in this study were female (63.86%), Caucasian (83.09%) and were 30 to 59 years of age (80.00%). The fact that more females participated in this study than male is not consistent with other survey studies in a similar population.[77, 80] The majority of participants were practicing in inpatient pharmacy settings (46.34%); this is likely due to the fact that the population of this study were preceptors of PharmD students who were primarily practicing in a hospital setting. In other similar studies, the majority of pharmacists were practicing in a community/outpatient pharmacy setting.[16, 80, 100]

This study found that the reporting rate of DS related AE is low. Less than 10% of participants indicated that they had included a DS in their AE report to the FDA MedWatch system and to a drug manufacturer. The reporting rate of DS related AE to the DS manufacturer was even less (5.34%). This low reporting rate of DS related AE in general might be due to participants' lack of knowledge of DS regulations. Also, the majority of participants did not know that the FDA requires the manufacturer (i.e., the entity that is manufacturing and labeling for initial sale or the entity that is repackaging products for sale) to report all serious DS related AEs to the FDA within 15 days. These findings are consistent with the FDA reports that about 38% of DS related AE reports were voluntary reports including all mild, moderate and serious DS related AE submitted by consumers and healthcare practitioners to the FDA. The majority of DS related AE reports (62%) were mandatory reports of serious AEs submitted by DS manufacturer.[15]

The percentage of participants who had completed formal training related to DS or CAM is about 20%. That is relatively low considering that about 40% of participants have encountered a patient with a suspected DS related AE. Our finding is lower than Chang et al. who found that about 45% of a convenience sample of practicing pharmacists attending regional meetings had previous continuing education on herbal medications.[100] Another study found that about 56% of practicing pharmacists in California had previous training on CAM.[101] In a study by Olatunde et al., pharmacy leaders were interviewed to assess their perceptions of pharmacists' professional roles and responsibilities about NHP. Pharmacy leaders described pharmacists' professional roles and responsibilities for NHPs as similar to those for OTC drugs and believed that pharmacists should have a basic level of knowledge about NHPs and NHP regulations. They also stated that pharmacy managers should provide additional training to ensure that their pharmacists have sufficient knowledge of NHPs sold in the pharmacy.[102] The low percentage of practicing pharmacists who completed formal training on DS might indicate the shortage of such courses and programs that are available for pharmacists and other healthcare professionals as continuing education credits.

The overall participants' attitudes toward the clinical use of DS tended to be positive (41.10%) or neutral (25.90%). Their overall attitude toward the safety of DS, on the other hand, tended to be negative (41.50%) or neutral (32.10%). A systematic review of 19 studies of U.S. and Canadian pharmacists reported inconsistent attitudes of pharmacists toward the clinical efficacy and safety of DS. Both positive and negative attitudes were reported and no clear conclusion was drawn due to heterogeneity of the included study

results and lack of a consistent definition of DS.[71] The finding of this study related to pharmacist's attitudes toward the efficacy and safety of DS contradict the findings of two previous U.S. studies.[16, 101] Dolder et al. found that about 50% of practicing pharmacists in California had a negative attitude toward safety of DS.[101] About 19% of practicing pharmacists in Minnesota believed that HNP were effective for clinical use and about 50% believed they were safe.[16] This study found that formal training related to DS or CAM significantly affected pharmacist's overall attitude toward the clinical use and safety of DS. Formal training increased positive attitudes toward the clinical use of DS and increased the negative attitude regarding the safety of DS. This might be due to formal training increasing pharmacist's overall awareness of the evidence of the effectiveness of some DS products, on one hand, as well as increasing pharmacist's awareness of the potential risks associated with the consumption of some DS products related to DS contamination or interactions with other medication.

Evaluation of DS knowledge in this study was not comprehensive and might not have correctly measured the actual participants' knowledge about DS. The ability of practicing pharmacist to correctly identify a DS product was evaluated. The average DS identification quiz score was 80%. This is not consistent with the findings of the only other identified U.S. study that assessed pharmacist's actual knowledge of DS. The average score in that study was less than 50%. The significant difference between the average score in that study and this study may be due to the difference in the comprehensiveness and difficulty level of the two tests. The test in the aforementioned study was more comprehensive. Also, participants of that study were instructed to select "I don't know"

instead of guessing an answer.[71] More research is needed to assess pharmacist and other healthcare professional knowledge about the use of DS. The assessment should include knowledge about DS indication, effectiveness, dosage, storage, side effects, DS-DS interactions, and DS-drug interactions.

The average pharmacist's knowledge score on DS regulations quiz was about 46% in this study. Ashar et al. evaluated physician knowledge of DS regulation and the AE reporting process. The average knowledge score was poor (59%).[54] Another study by the same group found that the average knowledge score of 15 medical residents of DS regulation was about 60%.[78] No studies evaluated pharmacist knowledge of DS regulations. Courses on DS regulation could increase healthcare professionals' awareness of such regulation and the reporting process of DS related AE. Physicians' average scores dramatically increased to from 59% to 91% after completing an online course about DS regulation.

DS Information Resources

The most commonly used DS information resources according to the current study were Lexi-Comp® (69.90%), Facts and Comparisons: Review of Natural Products (61.65%), Natural Medicines Comprehensive Database (by Pharmacist's Letter) (57.77%), and Micromedex®: AltMedDex (47.57%). These four most commonly used resources were those most commonly held at practice site. These findings are consistent with Bazzie et al. study where they found the most commonly used DS information resources in acute care facilities were the internet (66%), Natural Medicines Comprehensive Database (34%),

and Micromedex®: AltMeDex (23%).[99] The most commonly available resources in another study were different than our finding; Nathan et al. found that the most commonly used DS information resources in community pharmacies in New York and New Jersey were the PDR for Herbal Medicines (42.5%), The Review of Natural Products (20.0%), and the Web site of the National Center for Complementary and Alternative Medicine (12.5%).[61]

Publication dates of popular DS information resources varied considerably. Three of the most commonly used resources in this study were fairly timely updated: Lexi-Comp® is an online recourse that is updated automatically on daily bases and Micromedex®: AltMeDex is an electronic resource that is updated annually. The print version of Natural Medicine Comprehensive Database is updated annually, and portions of The Review of Natural Products are updated monthly. The timeliness of these resources is important, as information in this field is changing rapidly. Also, the three most commonly used resources were both available in electronic formats, possibly indicating that the ability to easily search by a variety of common names, as well as by popular brand-name formulations, may be important factors for administrators in selecting information resources. Resources available in electronic formats may also be preferred because their content is updated more frequently than that of print texts.

All of the resources were relatively useful with the minimum score of 3.03 and maximum score 4.21 out of 5. The most useful resource was Natural Medicines Comprehensive Database followed by The Complete German Commission E Monographs and Facts and Comparisons: Review of Natural Products. However, the second most useful

resource, The Complete German Commission E Monographs, is relatively old. It was published in 1998 and is a translation of an earlier work. No other studies evaluated the usefulness of these resources as source of information about DS. These resources might be different in providing good summaries of available literature, addressing the possible side effects, contraindications, DS-drug interactions, or DS-DS interactions. Further evaluation of the usefulness of DS information resources in answering specific DS related questions is needed.

Conjoint Analysis

To the best of our knowledge, there has been no previous research done to identify factors affecting a pharmacist's decision in reporting a DS related AE to the FDA MedWatch system or other agencies. Practicing pharmacists were selected because they could be among the first line in detecting and reporting AEs related to the use of DS. Moreover, DS consumers consider pharmacists a reliable and knowledgeable source of information and advice about DS. In a U.S. study, 37% of respondents viewed pharmacists' advice CAM as important and 30 % of them relied on pharmacists as a source of information about the choices of DS and herbal products.[19, 103]

The CA portion of this study revealed that the most important attribute was the evidence supporting the AE in the literature for reporting to the prescriber. The second most important attribute was the outcome of the AE. The first and second most important attribute were opposite for reporting to the drug manufacturer, DS manufacturer and FDA MedWatch system. The outcome of the AE the most important attribute and the evidence

supporting the AE in the literature was the second most important. In general, all other attributes were much less important than these two attributes. This might indicate that practicing pharmacists think they need to provide strong evidence when calling the prescribing provider to report an AE. That also might indicate that the pharmacists perceive the outcome of the AE to be more important to the drug manufacturer, DS manufacturer, and FDA MedWatch system than the evidence supporting the AE when deciding whether to submit the AE report.

The relationship between the attributes levels were as expected for most of the attributes. The younger age category (25 years) and the elder age category (70 years) have higher utilization on pharmacists' decision than the middle age category (45 years). The closer initiation time of DS and change of drug therapy (2 weeks ago) have higher utilization on pharmacists' decision than the longer initiation of DS and change of drug therapy (6 months ago). Also, the permanent disability as the outcome of the AE has higher utilization on pharmacists' decision than the self-limited outcome.

It was expected that participants would place more importance on absence of evidence of the AE in the literature in reporting an AE to any place; especially to the FDA MedWatch system. All models, however, indicated the opposite. Participants cited availability of consistent evidence in the literature significant compared to the absence of evidence in reporting an AE to all places. This might indicate the need for more evidence on the efficacy and safety of DS. It might also indicate the need to educate professionals that absence of evidence in the literature maybe another compelling reason to submit an AE report. The importance that participants gave to the levels of the outcome of the AE

was as hypothesized. Participants reported less importance to the self-limited AE that resolved upon discontinuation of the DS and more importance to the serious AE that resulted in permanent disability.

Reporting of DS-AE to any place might be influenced by the propensity to report characteristic of the participant. Some people are "reporters" and some are not "reporters". This general reporting issue was assessed by asking participants if they had ever reported an AE to drug manufacturer, DS manufacturer or FDA MedWatch system. Reporting characteristic variables were included as covariates in the adjusted models in estimating the importance of the five selected attributes. Future research is needed to further examine the effect of propensity to report characteristic of a professional on decision to report a DS-AE.

The models did not perform well in predicting the holdout profile responses. However, models were better in predicting responses of the study profiles. The correlation between the predicted and actual responses was around 50% in all models. Generalization of these results should be made with care. Selection of a sample from the state of Virginia and from specific population of preceptors of PharmD student limits generalizability. The statistically insignificant coefficients of some attributes still might be of importance to the participants, but they merely do not perceive a detectable difference.[104]

Implications

As mentioned before, the reporting rate of AE related to DS by healthcare professionals to the FDA MedWatch system is as low as 1 % given their high consumption

rate in the United States.[48] The reporting to other agencies such as PCCs and DS manufacturers is most likely to be lower than expected. On the other hand the FDA MedWatch system does not have strict premarketing regulations and considers these products as generally safe unless proven otherwise through its MedWatch system.

Identifying the important factors influencing pharmacist's decisions to report a DS related AE might be helpful for authorities in establishing policies and regulations of the reporting process of DS related AE. This study found that the most important factors in reporting a DS related AE were the evidence supporting the AE in the literature and the severity of the AE outcome. However, the amount of evidence in the literature about DS is relatively low, likely in part, because the FDA does not require DS manufacturer to submit premarketing safety and efficacy studies. Also NIH and other Federal institutions fund relatively fewer DS studies compared to conventional drug studies. This study indicates that there is a need for more DS evidence in the literature to improve the reporting of DS related AE among pharmacists. Practicing pharmacist's knowledge of DS regulation is poor as indicated by this and other studies.[21, 36, 54, 55] Developing and providing education on DS for pharmacy students as well as for practicing pharmacists could be beneficial because this may improve their knowledge about DS and potentially increase their reporting of DS related AEs. The literature indicated that pharmacists themselves do not perceive their knowledge to be adequate and would like to receive additional education on DS.[16, 103]

The description of DS information resource usage, availability and usefulness could be used by healthcare systems and community pharmacy leaders as guidance in selecting

the best DS information resources for their institutions. According to the findings of this study, the most commonly used DS information recourses are not necessarily the most useful ones. Findings of this study might be used to improve the availability and usage of the most useful DS resources.

Strengths

One strength of the study was the assessment of five attributes related to patient factors, AE outcome, and other concomitant medications that were hypothesized to influence a pharmacist's decision in reporting a DS related AE. Another strength is the assessment of participating pharmacist's attitude, knowledge and other characteristics. This study also sought to analyze the impact of these characteristics as secondary factors on the utility and importance of the five primary attributes. Although the entire questionnaire had not been formally validated, the knowledge section was based on items that had been validated in previous studies.[28, 29, 78] Additionally, the results were generally intuitively correct and go along with the published literature. For instance, women had more positive attitude toward DS than men. This might lends some credibility and validity to the results of this study.

Limitations

This project has some limitations related to the sampling frame, validity of the design, validity the method and the instrument used in this study. Since the study population was limited to the Commonwealth of Virginia, the external validity of the study

and the generalizability of the findings to other states might be limited. In addition, the generalizability of our findings to other healthcare providers might be limited because our sampling frame is limited to practicing pharmacists. Additionally, the majority of respondents were female and Caucasian thus limiting generalizability to males and other ethnicities. The external validity of the study might be limited because the study sample was not a random sample. It is also possible that there may be unobserved factors introducing a systematic bias. The use of pharmacy preceptors as the population of interest might have added potential selection bias because these individuals might be more in tune with reporting than the general population of practicing pharmacists. A convenience sample was used to reduce the complexity and difficulty of the design. It was, also, difficult and unfeasible to select a nationwide random sample of practicing pharmacists since no known or readily available list of all practicing pharmacists in the nation exists.

Death as the most extreme outcome was not included as one of the levels because that would have required a different scenario template that could have confused the respondents. The omission of death as a potential outcome could confound the responses as the respondents could have thought that the "resulted in permanent disability" is not the most extreme outcome. This issue was extensively discussed with a group of practicing pharmacists in the process of developing the questionnaire. After discussion, it was concluded that either death or permanent disability would be sufficiently the same from this standpoint. The responses could however be different if death were included.

Some of the variables that are not the focus of this study such as patient gender and ethnicity were held constant to keep the scenarios concise and manageable by respondents.

Clinical information that could be important in such decision making is not provided in the scenarios. This was done to reduce the complexity of the scenarios and to make the choice task manageable by the respondents. It has been suggested that up to six variables could be handled by respondents in one scenario.[96] These issues might limit the ability of these scenarios to reflect the actual pharmacist's decisions to report DS-AE. Another limitation could be related to the exclusion of pregnant and breastfeeding women. While including this group might have influenced DS-AE reporting given risk to the infant, it would have introduced another level of complexity that could further complicate the scenarios. To avoid the confusion that might happen in the minds of the participants when they consider such population, male gender was used rather than female gender or both male and female gender.

Due to the nature of this type of preference study, it is unknown whether or not the responses to hypothetical case scenarios' questions would reflect what respondent might actually do in a real situation. The purpose of adding the holdout scenarios was to help assure the validity of the responses and to minimize this limitation.[88, 98, 105] However, the model was not good in predicting responses for the holdout profiles. The general purpose of this study was understating the importance of the five selected attributes on participating pharmacists' decision to report a DS-AE. It was not proposed to predict responses in other population.

As a general limitation of the preference studies such as this study, there is a potential for domination of few attributes in making a decision or a preference. Sometimes individuals for various reasons such as the inclusion of too many attributes or lack of

understanding of the situation or just for their general decision-making process will only focus on one or two attributes. These attributes then dominate the other attributes. In this study, the evidence of AE and the outcome of the AE seem to be dominant attributes over the other attributes. Future studies might be needed to look at this potential phenomenon.

The items examining the pharmacist's knowledge about DS and their regulation were developed based on previous studies that assessed healthcare professional's knowledge about DS as well as group discussions with practicing pharmacists.[16, 28, 29, 54, 71, 80, 100] While the instrument used in this study was pre-tested to identify any potential problems, it's validity was not further examined. Additionally, because it was not a central focus of the study, the DS identification quiz was not comprehensive and may not have adequately measured the participant's knowledge about DS.

Future Directions

The findings from the descriptive portion of this study provide useful information on the general characteristics of practicing pharmacists about DS AE reporting that can be used as a foundation for generating hypotheses for future research in pharmacists and other healthcare professionals as well as consumers of DS. This study also attempted to evaluate attributes affecting pharmacist decision making in reporting an AE related to DS uses. Future studies could be conducted to evaluate attributes influencing these decisions in physicians and other healthcare professionals. No other similar studies were identified in the literature. Further research is needed to further investigate the main objectives of this study and to further confirm its findings. This research also highlights the need to develop

educational tools and strategies to improve the knowledge of pharmacists related to DS and DS regulation.

Conclusion

The overall attitude of practicing pharmacists was relatively positive for the clinical use of DS but relatively negative for safe of DS. Formal training on DS is associated with better knowledge regarding DS regulation. Very few people included DS in an ADE report to either the FDA MedWatch system or the drug manufacturer and almost none had ever reported an AE to a DS manufacturer. The average knowledge score of DS identification was relatively good but is low for DS regulation knowledge. More comprehensive DS knowledge assessment of pharmacists and other healthcare professionals is needed. The usefulness and availability of DS information resources are variable. Lexi-Comp® is widely used and available information resource and the Natural Medicines Comprehensive Database is the most useful information resource. Most of these finding go along with available literature.

In general, the part worth values and the importance for the evidence supporting the AE and the severity of the outcome of the AE attributes were much higher than those of age of patient, initiation of DS and time since last modification of drug therapy attributes. The important level of the attributes that a pharmacist considered in the decision to report a DS-AE to the drug manufacturer, DS manufacturer and FDA MedWatch system classified into three levels. Outcome of the AE had high importance level, the evidence of the AE had medium importance level, and the remaining three attributes (age of patient, initiation

of DS and time since last modification of drug therapy) had low importance level. The importance levels of the attributes classified into two levels only when reporting to the prescriber. Both evidence of the AE and outcome of the AE had high importance level and the remaining three attributes had low importance level.

Literature Cited

Literature Cited

1. Millen AE, Dodd KW, Subar AF. Use of vitamin, mineral, nonvitamin, and nonmineral supplements in the United States: The 1987, 1992, and 2000 National Health Interview Survey results. *J Am Diet Assoc*. 2004;104:942-950.

2. Slesinski MJ, Subar AF, Kahle LL. Trends in use of vitamin and mineral supplements in the United State: the 1987 and 1992 National Health Interview Surveys. *J Am Diet Assoc*. 1995;95:921-923.

3. Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clin Ther*. 2011;33:1749-1758.

4. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol*. 2004;160:339-349.

5. Ervin RB, Wright JD, Reed-Gillette D. Prevalence of leading types of dietary supplements used in the Third National Health and Nutrition Examination Survey, 1988-94. *Adv Data*. 2004;(349):1-7.

6. FDA Should Take Further Actions to Improve Oversight and Consumer Understanding. U.S. Government Accountability Office, Dietary Supplements; 2009;GAO-09-250. Available from: http://www.gao.gov/assets/290/285372.pdf. Accessed 04/017/2012.

7. Dietary Supplement Health and Education Act of 1994. U.S. Food and Drug Administration (FDA); 1994;Pub L No. 10S-417 (codified at 42 USC 287C-11). Available from: http://ods.od.nih.gov/about/dshea_wording.aspx. Accessed 04/017/2012.

8. Shaw D, Palmer ME. US Poisons Control Centers and reports of adverse events associated with dietary supplements. *Focus Altern Complement Ther*. 2003;8:317-319.

9. Van Strater AC, Bogers JP. Interaction of St John's wort (Hypericum perforatum) with clozapine. *Int Clin Psychopharmacol*. 2012;27:121-124.

10. Moyad MA. Under-hyped and over-hyped drug-dietary supplement interactions and issues. *Urol Nurs*. 2010;30:85-87.

11. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. *Drugs*. 2009;69:1777-1798.

12. Kailin D. The Dietary Supplement and Nonprescription Drug Consumer Protection Act. *California Journal of Oriental Medicine (CJOM)*. 2008;19:3.

13. Dietary Supplement Current Good Manufacturing Practices (cGMPs). Available at: http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm110858.htm. Accessed 4/23/2011, 2011.

14. Hopkinson SE. FDA announces MedWatch: a new reporting program for health professionals. *AANA J*. 1993;61:373-378.

15. Frankos VH, Street DA, O'Neill RK. FDA regulation of dietary supplements and requirements regarding adverse event reporting. *Clin Pharmacol Ther*. 2010;87:239-244.

16. Welna EM, Hadsall RS, Schommer JC. Pharmacists' personal use, professional practice behaviors, and perceptions regarding herbal and other natural products. *J Am Pharm Assoc*. 2003;43:602-611.

17. Gardiner P, Sarma DN, Low Dog T, et al. The state of dietary supplement adverse event reporting in the United States. *Pharmacoepidemiol Drug Saf*. 2008;17:962-970.

18. Irujo M, Beitia G, Bes-Rastrollo M, Figueiras A, Hernandez-Diaz S, Lasheras B. Factors that influence under-reporting of suspected adverse drug reactions among community pharmacists in a Spanish region. *Drug Saf*. 2007;30:1073-1082.

19. Levy S. `Healthcare 2000' reveals consumer view of RPhs. *Drug Topics*. 1999;143:64-65.

20. What Is Complementary and Alternative Medicine? Available at: http://nccam.nih.gov/health/whatiscam/. Accessed 8/02/2012.

21. Dodge T, Litt D, Kaufman A. Influence of the dietary supplement health and education act on consumer beliefs about the safety and effectiveness of dietary supplements. *J Health Commun*. 2011;16:230-244.

22. Hathcock J. Dietary supplements: how they are used and regulated. *J Nutr*. 2001;131:1114S-1117S.

23. Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: Prevalence of use and reports of adverse events. *J Am Diet Assoc*. 2006;106:1966-1974.

24. Picciano MF, Dwyer JT, Radimer KL, et al. Dietary supplement use among infants, children, and adolescents in the United States, 1999-2002. *Arch Pediatr Adolesc Med*. 2007;161:978-985.

25. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008;300:2867-2878.

26. Michaud LB, Karpinski JP, Jones KL, Espirito J. Dietary supplements in patients with cancer: risks and key concepts, part 2. *Am J Health Syst Pharm (AJHP)*. 2007;64:467-480.

27. Buettner C, Phillips RS, Davis RB, Gardiner P, Mittleman MA. Use of dietary supplements among United States adults with coronary artery disease and atherosclerotic risks. *Am J Cardiol*. 2007;99:661-666.

28. Gardiner P, Woods C, Kemper KJ. Dietary supplement use among health care professionals enrolled in an online curriculum on herbs and dietary supplements. *BMC Complement Altern Med*. 2006;6:21: 1-8.

29. Gardiner P, Legedza A, Woods C, Phillips RS, Kemper KJ. Herb use among health care professionals enrolled in an online curriculum on herbs and dietary supplements. *J Herb Pharmacother*. 2006;6:51-64.

30. Scott GN, Elmer GW. Update on natural product-drug interactions. *Am J Health Syst Pharm*. 2002;59:339-347.

31. Blumenthal M. FDA Announces Ban on Ephedra Supplements: Federal Move Follows Bans by California, Illinois and New York. *HerbalGram*. 2004:54-63.

32. President Signs New Law to Require Reporting of Serious Adverse Events of Dietary Supplements and OTC Drugs. *HerbalGram*. 2007:23-23.

33. Noah BA. A Review of the New York State Task Force on Life and the Law's Report: Dietary Supplements: Balancing Consumer Choice and Safety. *Journal of Law, Medicine & Ethics*. 2005;33:860-865.

34. Dietary Supplements: An Advertising Guide for Industry. Available at: http://business.ftc.gov/documents/bus09-dietary-supplements-advertising-guide-industry. Accessed 4/19/2012.

35. Bonakdar RA. Herbal cancer cures on the Web: noncompliance with The Dietary Supplement Health and Education Act. *Fam Med*. 2002;34:522-527.

36. Office of Dietary Supplements (ODS) Available at: http://ods.od.nih.gov/. Accessed 4/19/2012.

37. Wolff T, Witkop CT, Miller T, Syed SB, U.S. Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;150:632-639.

38. Lanham-New SA. Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment. *Proc Nutr Soc*. 2008;67:163-176.

39. Genaro Pde S, Martini LA. Vitamin A supplementation and risk of skeletal fracture. *Nutr Rev*. 2004;62:65-67.

40. Lindgren CE, Walker LA, Bolton P. L-tryptophan induced eosinophilia-myalgia syndrome. *J R Soc Health*. 1991;111:29-30.

41. Brulotte J, Vohra S. Epidemiology of NHP-drug interactions: identification and evaluation. *Curr Drug Metab*. 2008;9:1049-1054.

42. Shekelle P, Morton S, Hardy ML. Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease. *Evid Rep Technol Assess (Summ)*. 2003:1.

43. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833-1838.

44. Rodale. Consumer use of dietary supplements. *Prevention Magazine*. 1999.

45. Goldman RD, Rogovik AL, Lai D, Vohra S. Potential interactions of drug-natural health products and natural health products-natural health products among children. *J Pediatr*. 2008;152:521-6, 526.e1-4.

46. Ernst E. St John's Wort supplements endanger the success of organ transplantation. *Arch Surg*. 2002;137:316-319.

47. Whitten DL, Myers SP, Hawrelak JA, Wohlmuth H. The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol*. 2006;62:512-526.

48. Adverse Event Reporting For Dietary Supplements: An Inadequate Safety Valve. Washington D.C.: Department of Health and Human Services, Office of Inspector General; 2001 April;01-00-00180. Available from: http://oig.hhs.gov/oei/reports/oei-01-00-00180.pdf. Accessed 8/3/2012.

49. Robinson A, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med*. 2004;12:90-98.

50. Busse JW, Heaton G, Wu P, Wilson KR, Mills EJ. Disclosure of Natural Product Use to Primary Care Physicians: A Cross-sectional Survey of Naturopathic Clinic Attendees. *Mayo Clin Proc*. 2005;80:616-622.

51. Gardiner P, Graham RE, Legedza AT, Eisenberg DM, Phillips RS. Factors associated with dietary supplement use among prescription medication users. *Arch Intern Med*. 2006;166:1968-1974.

52. Pillitteri J, Shiffman S, Rohay J, Harkins A, Burton S, Wadden T. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity*. 2008;16:790-796.

53. Dodge T, Kaufman A. What makes consumers think dietary supplements are safe and effective? The role of disclaimers and FDA approval. *Health Psychol*. 2007;26:513-517.

54. Ashar BH, Rice TN, Sisson SD. Physicians' understanding of the regulation of dietary supplements. *Arch Intern Med*. 2007;167:966-969.

55. Kemper KJ, Gardiner P, Gobble J, Woods C. Expertise about herbs and dietary supplements among diverse health professionals. *BMC Complement Altern Med*. 2006;6:15.

56. Kiefer D, Shah S, Gardiner P, Wechkin H. Finding information on herbal therapy: a guide to useful sources for clinicians. *Altern Ther Health Med*. 2001;7:74-78.

57. Sweet BV, Gay WE, Leady MA, Stumpf JL. Usefulness of herbal and dietary supplement references. *Ann Pharmacother*. 2003;37:494-499.

58. Walker JB. Evaluation of the ability of seven herbal resources to answer questions about herbal products asked in drug information centers. *Pharmacotherapy*. 2002;22:1611-1615.

59. Boehm K, Raak C, Vollmar HC, Ostermann T. An overview of 45 published database resources for complementary and alternative medicine. *Health Info Libr J*. 2010;27:93-105.

60. Clauson KA, Polen HH, Peak AS, Marsh WA, DiScala SL. Clinical decision support tools: personal digital assistant versus online dietary supplement databases. *Ann Pharmacother*. 2008;42:1592-1599.

61. Nathan JP, Cicero LA, Koumis T, Rosenberg JM, Feifer S, Maltz F. Availability of and attitudes toward resources on alternative medicine products in the community pharmacy setting. *J Am Pharm Assoc (2003)*. 2005;45:734-739.

62. Shields KM, McQueen CE, Bryant PJ. National survey of dietary supplement resources at drug information centers. *J Am Pharm Assoc (2003)*. 2004;44:36-40.

63. Herbold NH, Vazquez IM, Goodman E, Emans SJ. Vitamin, Mineral, Herbal, and Other Supplement Use by Adolescents. *Topics in Clinical Nutrition*. 2004;19:266-272.

64. Neuhouser ML, Patterson RE, Levy L. Motivations for using vitamin and mineral supplements. *J Am Diet Assoc*. 1999;99:851-854.

65. Woolf A, Litovitz T. Reporting of adverse events. *N Engl J Med*. 2003;348:1410-1411.

66. Bronstein AC, Spyker DA, Cantilena LR,Jr, Green JL, Rumack BH, Dart RC. 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol (Phila)*. 2011;49:910-941.

67. Litovitz T. The TESS database. Use in product safety assessment. *Drug Saf*. 1998;18:9-19.

68. Kingston R, Blumenthal M. A Rational Perspective on Adverse Events Reports on Herbs: Misinterpretation of Adverse Reactions Tabulated in the TESS Annual Report of the American Association of Poison jControl Centers as They Relate to Ephedra Dietary Supplements. *HerbalGram*. 2003:48-53.

69. Woolf AD, Watson WA, Smolinske S, Litovitz T. The severity of toxic reactions to ephedra: comparisons to other botanical products and national trends from 1993-2002. *Clin Toxicol (Phila)*. 2005;43:347-355.

70. Suchard JR, Suchard MA, Steinfeldt JL. Physician knowledge of herbal toxicities and adverse herb-drug interactions. *Eur J Emerg Med*. 2004;11:193-197.

71. Kwan D, Hirschkorn K, Boon H. U.S. and Canadian pharmacists' attitudes, knowledge, and professional practice behaviors toward dietary supplements: a systematic review. *BMC Complement Altern Med*. 2006;6:31.

72. Blumenthal M. Kava safety questioned due to case reports of liver toxicity. *HerbalGram*. 2002:26-32.

73. Kava kava may cause irreversible liver damage. *S Afr Med J*. 2002;92:961.

74. Maglione M, Miotto K, Iguchi M, Jungvig L, Morton SC, Shekelle PG. Psychiatric effects of ephedra use: an analysis of Food and Drug Administration reports of adverse events. *Am J Psychiatry*. 2005;162:189-191.

75. Dennehy CE, Tsourounis C, Horn AJ. Dietary supplement-related adverse events reported to the California Poison Control System. *Am J Health Syst Pharm*. 2005;62:1476-1482.

76. Litovitz TL, Klein-Schwartz W, White S, et al. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 2000;18:517-574.

77. Cuzzolin L, Benoni G. Attitudes and knowledge toward natural products safety in the pharmacy setting: an Italian study. *Phytother Res*. 2009;23:1018-1023.

78. Ashar BH, Rice TN, Sisson SD. Medical residents' knowledge of dietary supplements. *South Med J*. 2008;101:996-1000.

79. Ashar BH, Miller RG, Pichard CP, Levine R, Wright SM. Patients' understanding of the regulation of dietary supplements. *J Community Health*. 2008;33:22-30.

80. Zeolla MM, Cerulli J. Use of and familiarity with dietary supplement information references by practicing pharmacists. *J Am Pharm Assoc (JAPhA)*. 2008;48:401-404.

81. Pereira CC, Mulligan M, Bridges JF, Bishai D. Determinants of influenza vaccine purchasing decision in the US: a conjoint analysis. *Vaccine*. 2011;29:1443-1447.

82. Dillman DA, Smyth JD, Christian LM. *Internet, Mail, and Mixed-Mode Surveys : The Tailored Design Method.* 3rd ed. Hoboken, N.J.: Wiley & Sons; 2009.

83. Wong PS, Ko Y, Sklar GE. Identification and evaluation of pharmacists' commonly used drug information sources. *Ann Pharmacother*. 2009;43:347-352.

84. Qualtrics Online Survey Software | Enterprise Survey Tools Available at: http://www.qualtrics.com/. Accessed 7/20/2012.

85. Dietary Supplements - Reporting an Adverse Event. Available at: http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/ucm267384.htm. Accessed 7/20/2012.

86. Federal Food, Drug, and Cosmetic Act (FD&C Act) Available at: http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm. Accessed 7/20/2012.

87. Luce RD, Tukey JW. Simultaneous conjoint measurement: A new type of fundamental measurement. *J Math Psychol*. 1964;1:1-27.

88. Ryan M. Using conjoint analysis to take account of patient preferences and go beyond health outcomes: an application to in vitro fertilisation. *Soc Sci Med*. 1999;48:535-546.

89. Hailu G, Boecker A, Henson S, Cranfield J. Consumer valuation of functional foods and nutraceuticals in Canada. A conjoint study using probiotics. *Appetite*. 2009;52:257-265.

90. Bridges JF, Kinter ET, Kidane L, Heinzen RR, McCormick C. Things are Looking up Since We Started Listening to Patients: Trends in the Application of Conjoint Analysis in Health 1982-2007. *Patient*. 2008;1:273-282.

91. Franic DM, Haddock SM, Tucker LT, Wooten N. Pharmacy patronage: identifying key factors in the decision making process using the determinant attribute approach. *J Am Pharm Assoc (JAPhA)*. 2008;48:71-85.

92. Kievit W, van Hulst L, van Riel P, Fraenkel L. Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: results from a choice-based conjoint analysis. *Arthritis Care Res (Hoboken)*. 2010;62:842-847.

93. Latif A, Boardman H. Community pharmacists' attitudes towards medicines use reviews and factors affecting the numbers performed. *Pharm World Sci*. 2008;30:536-543.

94. O'Bryant CL, Crandell BC. Community pharmacists' knowledge of and attitudes toward oral chemotherapy. *J Am Pharm Assoc (JAPhA)*. 2008;48:632-639.

95. Hair JF. Conjoint analysis. In: *Multivariate Data Analysis with Readings.* 7th ed. Englewood Cliffs, N.J.: Prentice Hall; 2009:785, 12.

96. Orme BK. Which conjoint method should I use? In: Sawtooth Solutions. *Sawtooth Software, Inc*. 2007.

97. Bech M, Gyrd-Hansen D. Effects coding in discrete choice experiments. *Health Econ*. 2005;14:1079-1083.

98. Orme BK, Orme BK. *Getting Started with Conjoint Analysis : Strategies for Product Design and Pricing Research.* Madison, WI: Madison, WI : Research Publishers, LLC; 2006.

99. Bazzie KL, Witmer DR, Pinto B, Bush C, Clark J, Deffenbaugh J. National survey of dietary supplement policies in acute care facilities. *American Journal of Health-System Pharmacy.* American Society of Health System Pharmacists; 2006;63:65-70.

100. Chang ZG, Kennedy DT, Holdford DA, Small RE. Pharmacists' knowledge and attitudes toward herbal medicine. *Ann Pharmacother*. 2000;34:710-715.

101. Dolder C, Lacro J, Dolder N, Gregory P. Pharmacists' use of and attitudes and beliefs about alternative medications. *Am J Health Syst Pharm*. 2003;60:1352-1357.

102. Olatunde S, Boon H, Hirschkorn K, Welsh S, Bajcar J. Roles and responsibilities of pharmacists with respect to natural health products: key informant interviews. *Res Social Adm Pharm*. 2010;6:63-69.

103. Kwan D, Boon HS, Hirschkorn K, et al. Exploring consumer and pharmacist views on the professional role of the pharmacist with respect to natural health products: a study of focus groups. *BMC Complement Altern Med*. 2008;8:40.

104. Flynn TN, Louviere JJ, Peters TJ, Coast J. Best--worst scaling: What it can do for health care research and how to do it. *J Health Econ*. 2007;26:171-189.

105. Orme BK. Interpreting Conjoint Analysis Data. Available at: http://business.nmsu.edu/~mhyman/M310_Articles/Interpreting_CA_Data.pdf. Accessed 8/3/2012.

APPENDICES

APPENDIX A

Ranked Full Listing of Study Profiles

Table A.1 – Full listing of the study profiles used in final conjoint questionnaire sorted by their rank score for reporting to the prescriber

		Attributes					
	Block	Age of patient	Initiation of DS	Change of therapy	Evidence	Outcome	Rank†
1.	L3	25	2W	2W	KN	DIS	1.47
2.	E2	70	9M	2W	KN	DIS	1.25
3.	M2	45	2W	9M	KN	DIS	1.2
4.	I3	25	9M	9M	KN	DIS	1.19
5.	N4	45	9M	2W	KN	DIS	1.12
6.	G1	25	2W	9M	KN	HO	1.01
7.	K4	70	2W	9M	KN	HO	0.97
8.	B3	45	2W	2W	KN	HO	0.94
9.	F4	25	2W	2W	KN	ER	0.93
10.	B4	25	9M	2W	KN	HO	0.93
11.	G3	70	9M	2W	KN	HO	0.89
12.	A4	70	2W	2W	RPT	DIS	0.86
13.	E1	25	2W	9M	RPT	DIS	0.8
14.	I1	45	2W	9M	KN	ER	0.66
15.	J1	45	9M	9M	KN	HO	0.66
16.	B1	70	9M	9M	KN	ER	0.61
17.	D2	45	9M	2W	KN	ER	0.58
18.	C4	70	9M	9M	RPT	DIS	0.58
19.	M3	45	9M	2W	RPT	DIS	0.55
20.	F1	25	2W	2W	RPT	HO	0.54
21.	E4	70	9M	2W	RPT	HO	0.32
22.	H2	70	2W	2W	RPT	ER	0.32
23.	N2	45	2W	9M	RPT	HO	0.27
24.	M4	25	2W	9M	RPT	ER	0.26
25.	A2	25	9M	9M	RPT	HO	0.26
26.	J2	45	2W	2W	RPT	ER	0.19
27.	G2	25	9M	2W	RPT	ER	0.18
28.	C2	70	2W	2W	KN	SL	0.05
29.	A1	45	9M	9M	RPT	ER	-0.09
30.	K3	25	9M	2W	KN	SL	-0.09
31.	I2	70	2W	9M	UNK	DIS	-0.18
32.	D4	45	2W	9M	KN	SL	-0.18
33.	C3	45	2W	2W	UNK	DIS	-0.21
34.	M1	25	9M	2W	UNK	DIS	-0.22
35.	H4	70	9M	9M	KN	SL	-0.23
36.	E3	25	2W	2W	UNK	HO	-0.4

37.	J4	70	2W	2W	UNK	HO	-0.44
38.	H3	25	2W	2W	RPT	SL	-0.48
39.	L4	45	9M	9M	UNK	DIS	-0.49
40.	B2	25	2W	2W	UNK	ER	-0.58
41.	G4	70	2W	9M	RPT	SL	-0.62
42.	D3	45	2W	9M	UNK	HO	-0.67
43.	J3	70	9M	2W	RPT	SL	-0.7
44.	A3	70	2W	9M	UNK	ER	-0.72
45.	F3	70	9M	9M	UNK	HO	-0.72
46.	K1	45	9M	2W	UNK	HO	-0.75
47.	N3	25	9M	9M	RPT	SL	-0.76
48.	I4	70	9M	2W	UNK	ER	-0.8
49.	L2	45	9M	2W	RPT	SL	-0.83
50.	H1	25	9M	9M	UNK	ER	-0.86
51.	F2	45	9M	2W	UNK	ER	-0.93
52.	K2	70	2W	2W	UNK	SL	-1.46
53.	L1	25	2W	9M	UNK	SL	-1.52
54.	N1	45	2W	2W	UNK	SL	-1.59
55.	D1	25	9M	2W	UNK	SL	-1.65
56.	C1	45	9M	9M	UNK	SL	-1.87

25: 25 years; 45: 45 years; 70: 70 years; 2W: 2 months ago; 9M: 9 months ago; KN: Consistent evidence in the literature; RPT: inconsistent (or mixed) evidence; UNK: no evidence in the literature; SL: self-limiting and resolved upon discontinuation of dietary supplement; ER: required an ER visit; HO: required hospitalization; DIS: resulted in permanent disability.

†Is the sum of part-worth utilities of each profile

Table A.2 – Full listing of the study profiles used in final conjoint questionnaire sorted by their rank score for reporting to the drug manufacturer

		Attributes					
	Block	Age of patient	Initiation of DS	Change of therapy	Evidence	Outcome	Rank†
1.	L3	25	2W	2W	KN	DIS	1.50
2.	M2	45	2W	9M	KN	DIS	1.24
3.	A4	70	2W	2W	RPT	DIS	1.23
4.	E2	70	9M	2W	KN	DIS	1.23
5.	N4	45	9M	2W	KN	DIS	1.10
6.	E1	25	2W	9M	RPT	DIS	1.07
7.	I3	25	9M	9M	KN	DIS	1.06
8.	M3	45	9M	2W	RPT	DIS	0.82
9.	C4	70	9M	9M	RPT	DIS	0.79
10.	B3	45	2W	2W	KN	HO	0.64
11.	K4	70	2W	9M	KN	HO	0.61
12.	G1	25	2W	9M	KN	HO	0.60
13.	F4	25	2W	2W	KN	ER	0.48
14.	C3	45	2W	2W	UNK	DIS	0.48
15.	G3	70	9M	2W	KN	HO	0.47
16.	F1	25	2W	2W	RPT	HO	0.46
17.	B4	25	9M	2W	KN	HO	0.46
18.	I2	70	2W	9M	UNK	DIS	0.45
19.	M1	25	9M	2W	UNK	DIS	0.30
20.	I1	45	2W	9M	KN	ER	0.22
21.	H2	70	2W	2W	RPT	ER	0.21
22.	N2	45	2W	9M	RPT	HO	0.20
23.	J1	45	9M	9M	KN	HO	0.19
24.	E4	70	9M	2W	RPT	HO	0.19
25.	J2	45	2W	2W	RPT	ER	0.08
26.	D2	45	9M	2W	KN	ER	0.08
27.	B1	70	9M	9M	KN	ER	0.05
28.	M4	25	2W	9M	RPT	ER	0.04
29.	L4	45	9M	9M	UNK	DIS	0.03
30.	A2	25	9M	9M	RPT	HO	0.02
31.	G2	25	9M	2W	RPT	ER	-0.10
32.	C2	70	2W	2W	KN	SL	-0.10
33.	J4	70	2W	2W	UNK	HO	-0.15
34.	E3	25	2W	2W	UNK	HO	-0.16
35.	A1	45	9M	9M	RPT	ER	-0.36
36.	D4	45	2W	9M	KN	SL	-0.38

37.	H3	25	2W	2W	RPT	SL	-0.40
38.	K3	25	9M	2W	KN	SL	-0.41
39.	D3	45	2W	9M	UNK	HO	-0.43
40.	B2	25	2W	2W	UNK	ER	-0.43
41.	G4	70	2W	9M	RPT	SL	-0.54
42.	H4	70	9M	9M	KN	SL	-0.55
43.	K1	45	9M	2W	UNK	HO	-0.57
44.	A3	70	2W	9M	UNK	ER	-0.57
45.	F3	70	9M	9M	UNK	HO	-0.59
46.	J3	70	9M	2W	RPT	SL	-0.68
47.	I4	70	9M	2W	UNK	ER	-0.71
48.	L2	45	9M	2W	RPT	SL	-0.80
49.	F2	45	9M	2W	UNK	ER	-0.84
50.	N3	25	9M	9M	RPT	SL	-0.85
51.	H1	25	9M	9M	UNK	ER	-0.88
52.	K2	70	2W	2W	UNK	SL	-1.02
53.	N1	45	2W	2W	UNK	SL	-1.14
54.	L1	25	2W	9M	UNK	SL	-1.18
55.	D1	25	9M	2W	UNK	SL	-1.32
56.	C1	45	9M	9M	UNK	SL	-1.59

25: 25 years; 45: 45 years; 70: 70 years; 2W: 2 months ago; 9M: 9 months ago; KN: Consistent evidence in the literature; RPT: inconsistent (or mixed) evidence; UNK: no evidence in the literature; SL: self-limiting and resolved upon discontinuation of dietary supplement; ER: required an ER visit; HO: required hospitalization; DIS: resulted in permanent disability.

†Is the sum of part-worth utilities of each profile

Table A.3 – Full listing of the study profiles used in final conjoint questionnaire sorted by their rank score for reporting to the DS manufacturer

		Attributes					
	Block	Age of patient	Initiation of DS	Change of therapy	Evidence	Outcome	Rank†
1.	L3	25	2W	2W	KN	DIS	1.38
2.	E2	70	9M	2W	KN	DIS	1.37
3.	N4	45	9M	2W	KN	DIS	1.18
4.	M2	45	2W	9M	KN	DIS	1.10
5.	A4	70	2W	2W	RPT	DIS	1.10
6.	I3	25	9M	9M	KN	DIS	1.08
7.	E1	25	2W	9M	RPT	DIS	0.80
8.	M3	45	9M	2W	RPT	DIS	0.79
9.	C4	70	9M	9M	RPT	DIS	0.79
10.	G3	70	9M	2W	KN	HO	0.59
11.	B3	45	2W	2W	KN	HO	0.51
12.	K4	70	2W	9M	KN	HO	0.50
13.	B4	25	9M	2W	KN	HO	0.49
14.	C3	45	2W	2W	UNK	DIS	0.45
15.	I2	70	2W	9M	UNK	DIS	0.45
16.	M1	25	9M	2W	UNK	DIS	0.43
17.	G1	25	2W	9M	KN	HO	0.41
18.	F4	25	2W	2W	KN	ER	0.35
19.	F1	25	2W	2W	RPT	HO	0.21
20.	J1	45	9M	9M	KN	HO	0.20
21.	E4	70	9M	2W	RPT	HO	0.20
22.	D2	45	9M	2W	KN	ER	0.15
23.	B1	70	9M	9M	KN	ER	0.15
24.	L4	45	9M	9M	UNK	DIS	0.14
25.	I1	45	2W	9M	KN	ER	0.07
26.	H2	70	2W	2W	RPT	ER	0.07
27.	C2	70	2W	2W	KN	SL	0.00
28.	N2	45	2W	9M	RPT	HO	-0.07
29.	A2	25	9M	9M	RPT	HO	-0.09
30.	J2	45	2W	2W	RPT	ER	-0.12
31.	J4	70	2W	2W	UNK	HO	-0.14
32.	G2	25	9M	2W	RPT	ER	-0.14
33.	K3	25	9M	2W	KN	SL	-0.21
34.	M4	25	2W	9M	RPT	ER	-0.23
35.	E3	25	2W	2W	UNK	HO	-0.24
36.	H4	70	9M	9M	KN	SL	-0.30

37.	D4	45	2W	9M	KN	SL	-0.38
38.	A1	45	9M	9M	RPT	ER	-0.43
39.	K1	45	9M	2W	UNK	HO	-0.44
40.	F3	70	9M	9M	UNK	HO	-0.45
41.	H3	25	2W	2W	RPT	SL	-0.49
42.	B2	25	2W	2W	UNK	ER	-0.49
43.	J3	70	9M	2W	RPT	SL	-0.50
44.	I4	70	9M	2W	UNK	ER	-0.50
45.	D3	45	2W	9M	UNK	HO	-0.53
46.	G4	70	2W	9M	RPT	SL	-0.58
47.	A3	70	2W	9M	UNK	ER	-0.58
48.	L2	45	9M	2W	RPT	SL	-0.69
49.	F2	45	9M	2W	UNK	ER	-0.69
50.	N3	25	9M	9M	RPT	SL	-0.79
51.	H1	25	9M	9M	UNK	ER	-0.79
52.	K2	70	2W	2W	UNK	SL	-0.84
53.	N1	45	2W	2W	UNK	SL	-1.03
54.	D1	25	9M	2W	UNK	SL	-1.05
55.	L1	25	2W	9M	UNK	SL	-1.14
56.	C1	45	9M	9M	UNK	SL	-1.34

25: 25 years; 45: 45 years; 70: 70 years; 2W: 2 months ago; 9M: 9 months ago; KN: Consistent evidence in the literature; RPT: inconsistent (or mixed) evidence; UNK: no evidence in the literature; SL: self-limiting and resolved upon discontinuation of dietary supplement; ER: required an ER visit; HO: required hospitalization; DIS: resulted in permanent disability.

†Is the sum of part-worth utilities of each profile

Table A.4 – Full listing of the study profiles used in final conjoint questionnaire sorted by their rank score for reporting to FDA

		Attributes					
	Block	Age of patient	Initiation of DS	Change of therapy	Evidence	Outcome	Rank†
1.	L3	25	2W	2W	KN	DIS	1.65
2.	E2	70	9M	2W	KN	DIS	1.38
3.	M2	45	2W	9M	KN	DIS	1.34
4.	N4	45	9M	2W	KN	DIS	1.28
5.	I3	25	9M	9M	KN	DIS	1.19
6.	A4	70	2W	2W	RPT	DIS	1.18
7.	E1	25	2W	9M	RPT	DIS	0.98
8.	B3	45	2W	2W	KN	HO	0.91
9.	M3	45	9M	2W	RPT	DIS	0.82
10.	G1	25	2W	9M	KN	HO	0.81
11.	K4	70	2W	9M	KN	HO	0.81
12.	B4	25	9M	2W	KN	HO	0.75
13.	G3	70	9M	2W	KN	HO	0.75
14.	C4	70	9M	9M	RPT	DIS	0.72
15.	F4	25	2W	2W	KN	ER	0.63
16.	F1	25	2W	2W	RPT	HO	0.55
17.	J1	45	9M	9M	KN	HO	0.45
18.	C3	45	2W	2W	UNK	DIS	0.36
19.	I1	45	2W	9M	KN	ER	0.33
20.	E4	70	9M	2W	RPT	HO	0.28
21.	D2	45	9M	2W	KN	ER	0.27
22.	I2	70	2W	9M	UNK	DIS	0.26
23.	N2	45	2W	9M	RPT	HO	0.24
24.	M1	25	9M	2W	UNK	DIS	0.20
25.	B1	70	9M	9M	KN	ER	0.17
26.	H2	70	2W	2W	RPT	ER	0.16
27.	A2	25	9M	9M	RPT	HO	0.09
28.	J2	45	2W	2W	RPT	ER	0.06
29.	M4	25	2W	9M	RPT	ER	-0.03
30.	C2	70	2W	2W	KN	SL	-0.03
31.	G2	25	9M	2W	RPT	ER	-0.09
32.	L4	45	9M	9M	UNK	DIS	-0.10
33.	E3	25	2W	2W	UNK	HO	-0.17
34.	J4	70	2W	2W	UNK	HO	-0.18
35.	K3	25	9M	2W	KN	SL	-0.29
36.	D4	45	2W	9M	KN	SL	-0.33

37.	A1	45	9M	9M	RPT	ER	-0.39
38.	D3	45	2W	9M	UNK	HO	-0.48
39.	H4	70	9M	9M	KN	SL	-0.49
40.	H3	25	2W	2W	RPT	SL	-0.49
41.	K1	45	9M	2W	UNK	HO	-0.54
42.	B2	25	2W	2W	UNK	ER	-0.55
43.	F3	70	9M	9M	UNK	HO	-0.64
44.	G4	70	2W	9M	RPT	SL	-0.70
45.	J3	70	9M	2W	RPT	SL	-0.76
46.	A3	70	2W	9M	UNK	ER	-0.76
47.	I4	70	9M	2W	UNK	ER	-0.82
48.	L2	45	9M	2W	RPT	SL	-0.86
49.	F2	45	9M	2W	UNK	ER	-0.92
50.	N3	25	9M	9M	RPT	SL	-0.95
51.	H1	25	9M	9M	UNK	ER	-1.01
52.	K2	70	2W	2W	UNK	SL	-1.22
53.	N1	45	2W	2W	UNK	SL	-1.32
54.	L1	25	2W	9M	UNK	SL	-1.41
55.	D1	25	9M	2W	UNK	SL	-1.47
56.	C1	45	9M	9M	UNK	SL	-1.78

25: 25 years; 45: 45 years; 70: 70 years; 2W: 2 months ago; 9M: 9 months ago; KN: Consistent evidence in the literature; RPT: inconsistent (or mixed) evidence; UNK: no evidence in the literature; SL: self-limiting and resolved upon discontinuation of dietary supplement; ER: required an ER visit; HO: required hospitalization; DIS: resulted in permanent disability.

†Is the sum of part-worth utilities of each profile

APPENDIX B

Participant Information Sheet

VCU School of Pharmacy

Factors Influencing Pharmacists' Decision to Report Adverse Events Related to Dietary Supplements

Purpose and significance:

Previous research has shown that the reporting of adverse events related to dietary supplements by consumers and healthcare professionals is low as compared to their high consumption rate. There are many possible factors contributing to the low reporting rate of adverse events associated with the used of dietary supplements. Knowing these factors and their importance can be helpful in setting policies and regulations on reporting adverse events associated with the use of dietary supplements. It could also be helpful in developing educational programs to improve the awareness of healthcare professionals about dietary supplements. This study focuses on pharmacists as they could be among the first line in detecting and reporting adverse events associated with the use of dietary supplements.

The objectives of this study are to describe pharmacists' level of knowledge about dietary supplements and to determine the importance of selected factors that might influence a pharmacist's decision to report an adverse event associated with the use of dietary supplements.

Procedures:

By proceeding with the web based survey, you are agreeing to participate in this study. The questionnaire has three sections. You will first be provided with 5 case scenarios. Each scenario will be followed by four questions. Please read the scenarios and respond to the questions on the provided scale. Then you will be asked some questions about your knowledge of dietary supplements, their regulations and sources you might consult for dietary supplement information. The final section requests some basic demographic information.

Confidentiality:

This information is part of my dissertation project and your cooperation is greatly appreciated. Your answers will be held in strictest confidence on a secured web server at Virginia Commonwealth University. The records of this study will have no names or e-mail addresses attached during data collection or analysis. Any written results will discuss group findings and will not release any information that could possibly identify you as an individual.

Thank you very much for assisting me with my dissertation research. If you have any question, please contact me or my advisor.

Sincerely,
Ali Alhammad

Contact Information:

Ali Alhammad, M.S., PhD Candidate
VCU School of Pharmacy
Department of Pharmacotherapy and Outcomes Science
McGuire Hall Annex, Room 218
1112 E Clay St Richmond, VA 23298
Email: alhammada@vcu.edu
Phone: 804-628-3292
Fax: 804-628-3991

Spencer E. Harpe, PharmD, PhD, MPH
Associate Professor of Pharmacy Administration and Epidemiology & Community Health
VCU School of Pharmacy
Department of Pharmacotherapy and Outcomes Science
P.O. Box 980533
1112 E Clay St Richmond, VA 23298
Email: alhammada@vcu.edu
Phone: 804-828-3245
Fax: 804-628-3991

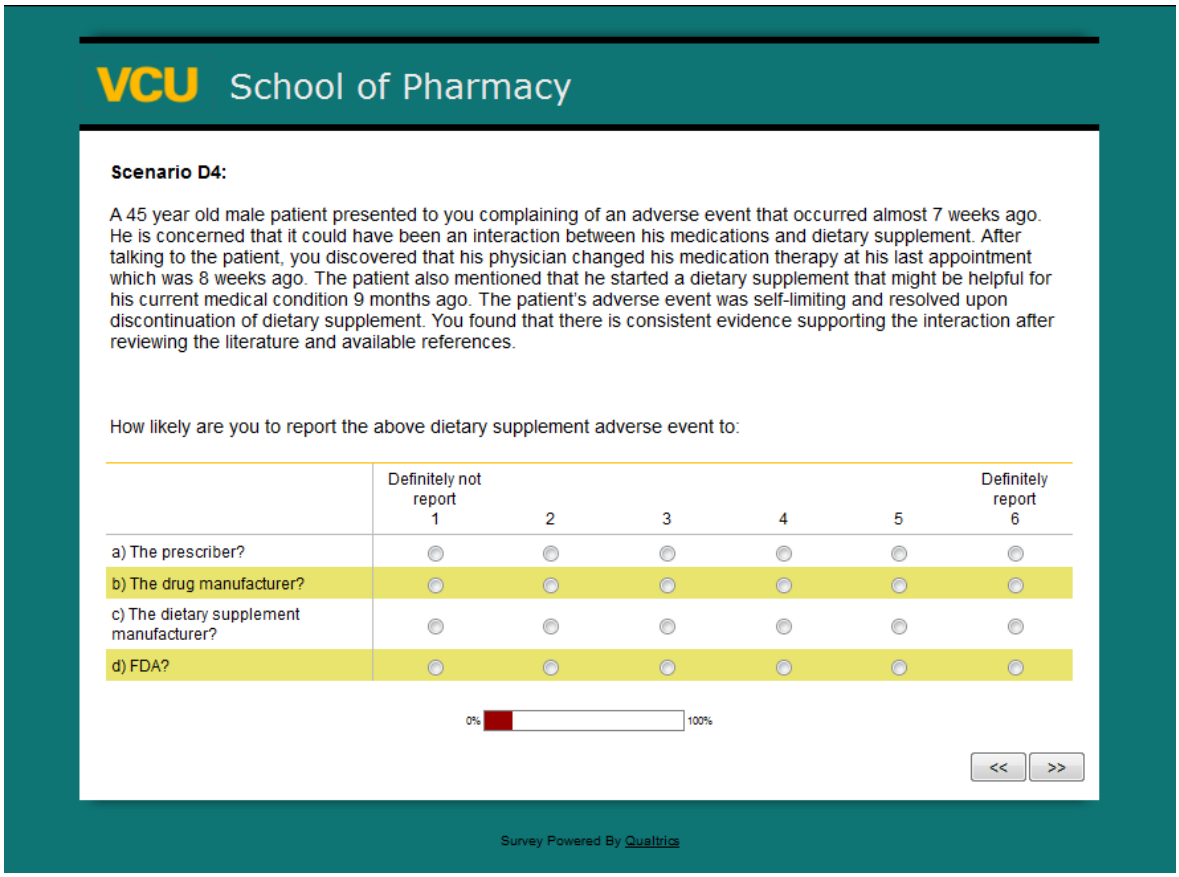
0% 100%

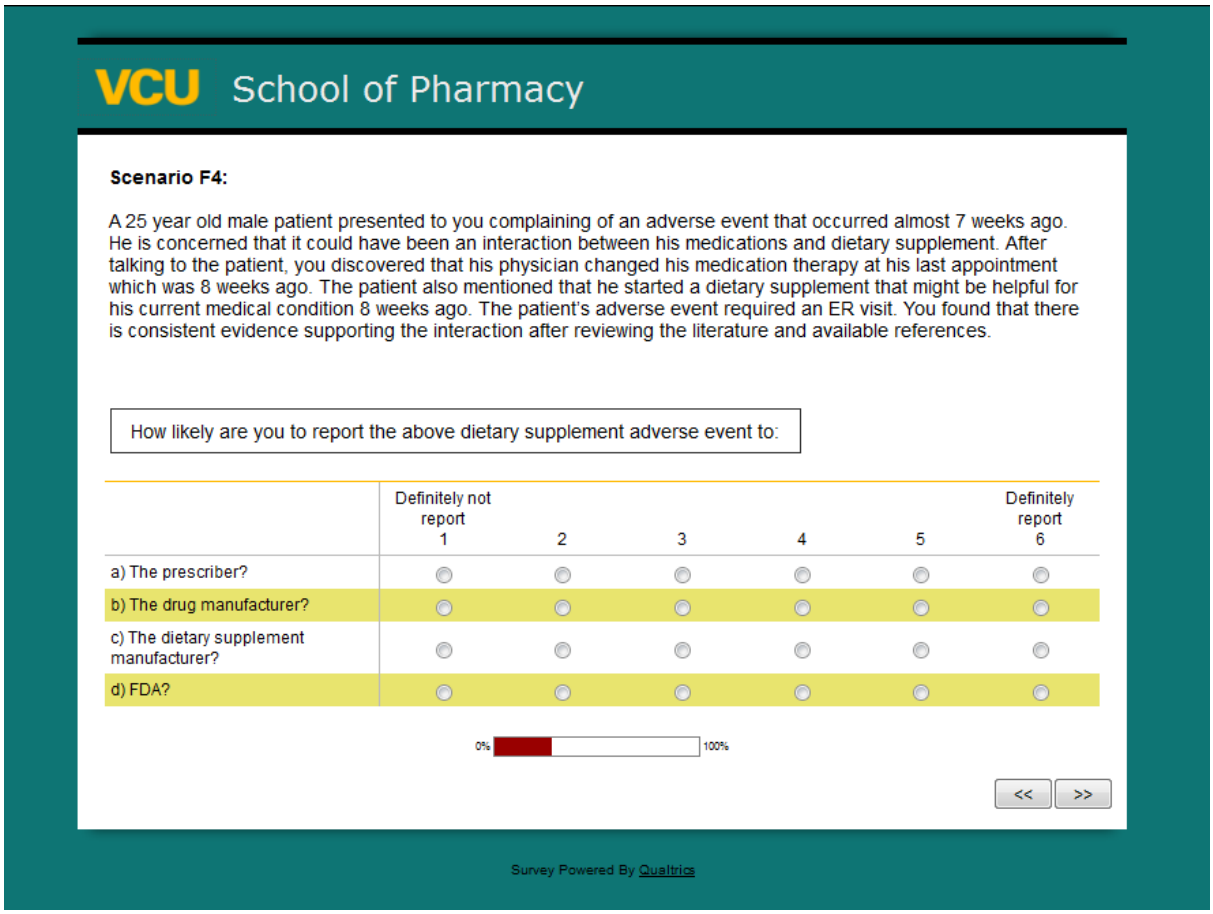
>>

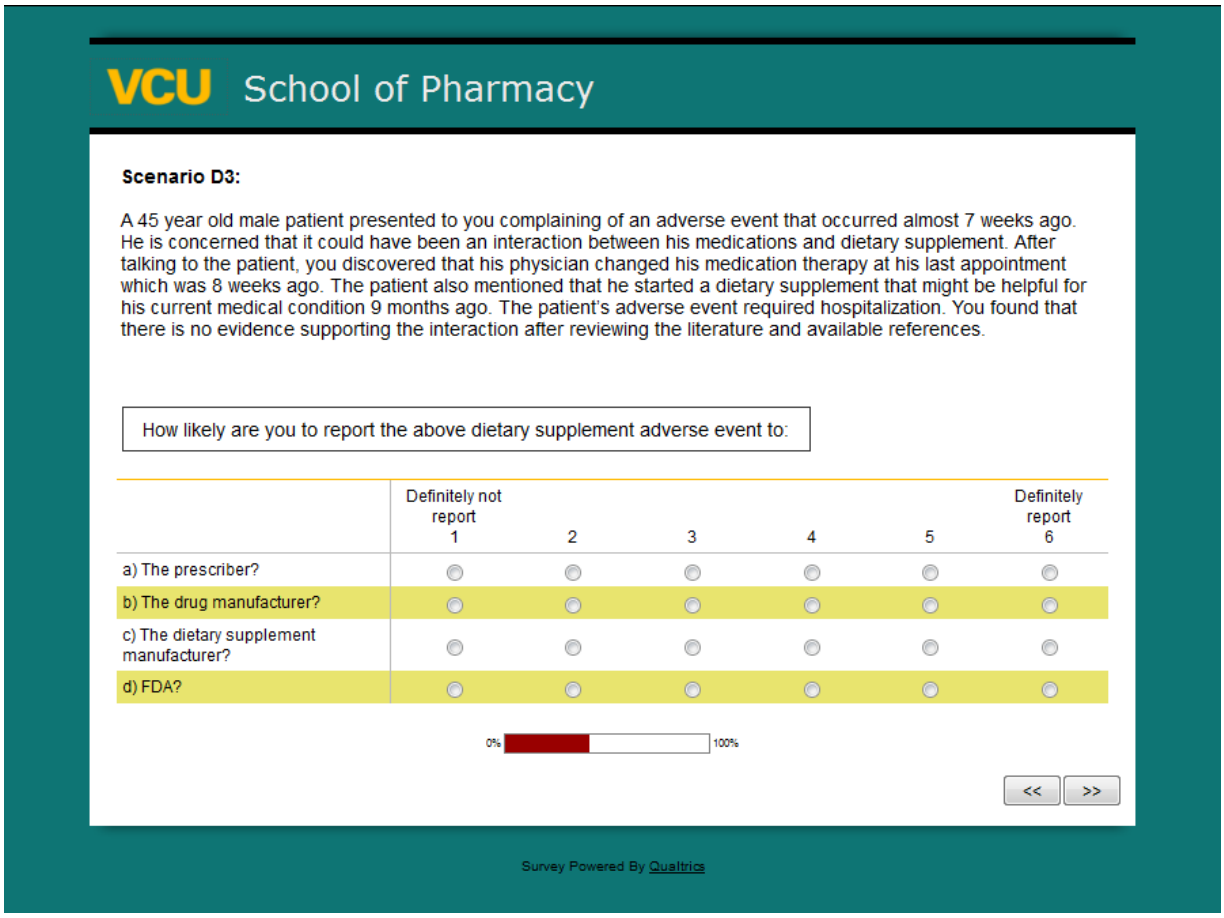
Survey Powered By Qualtrics

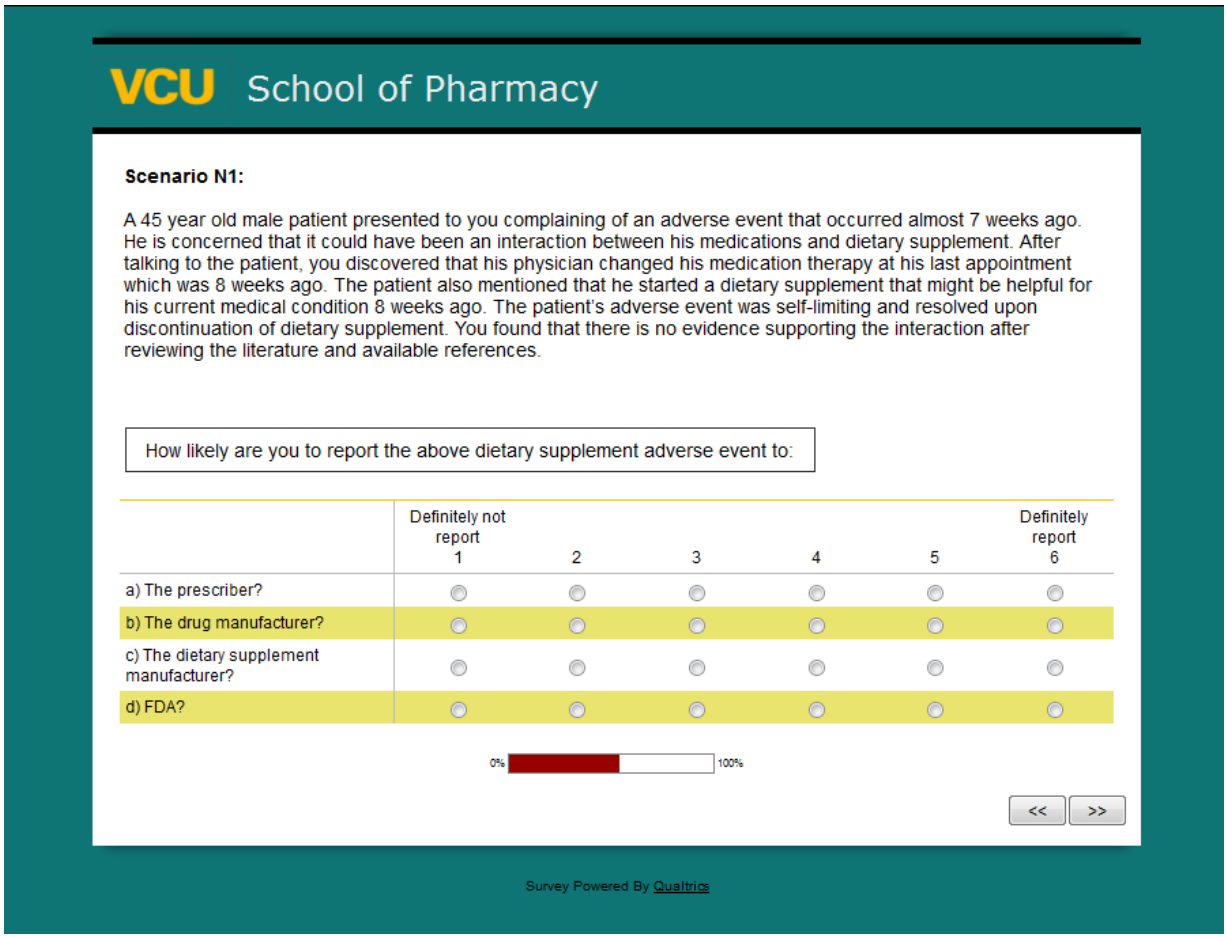
APPENDIX C

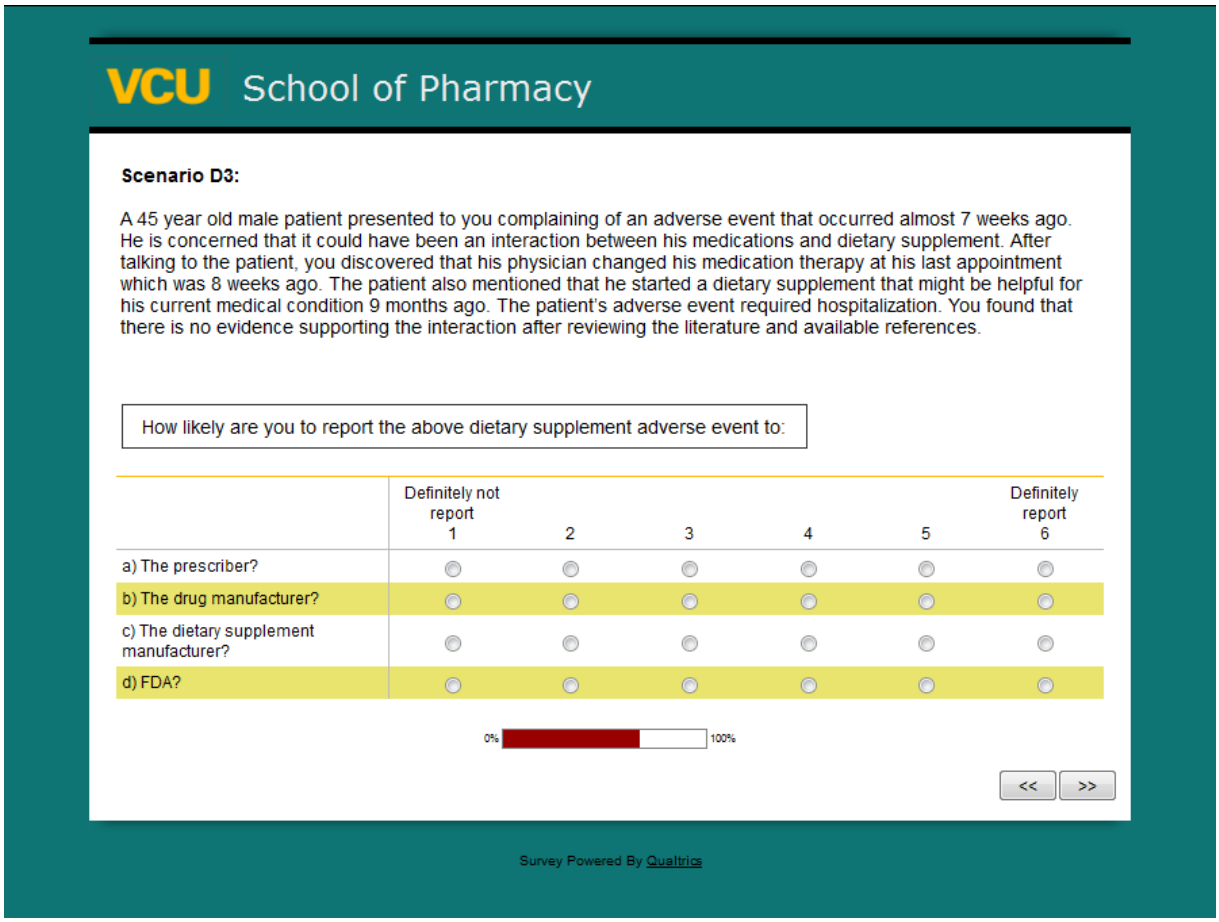
Screen Prints of the Questionnaire

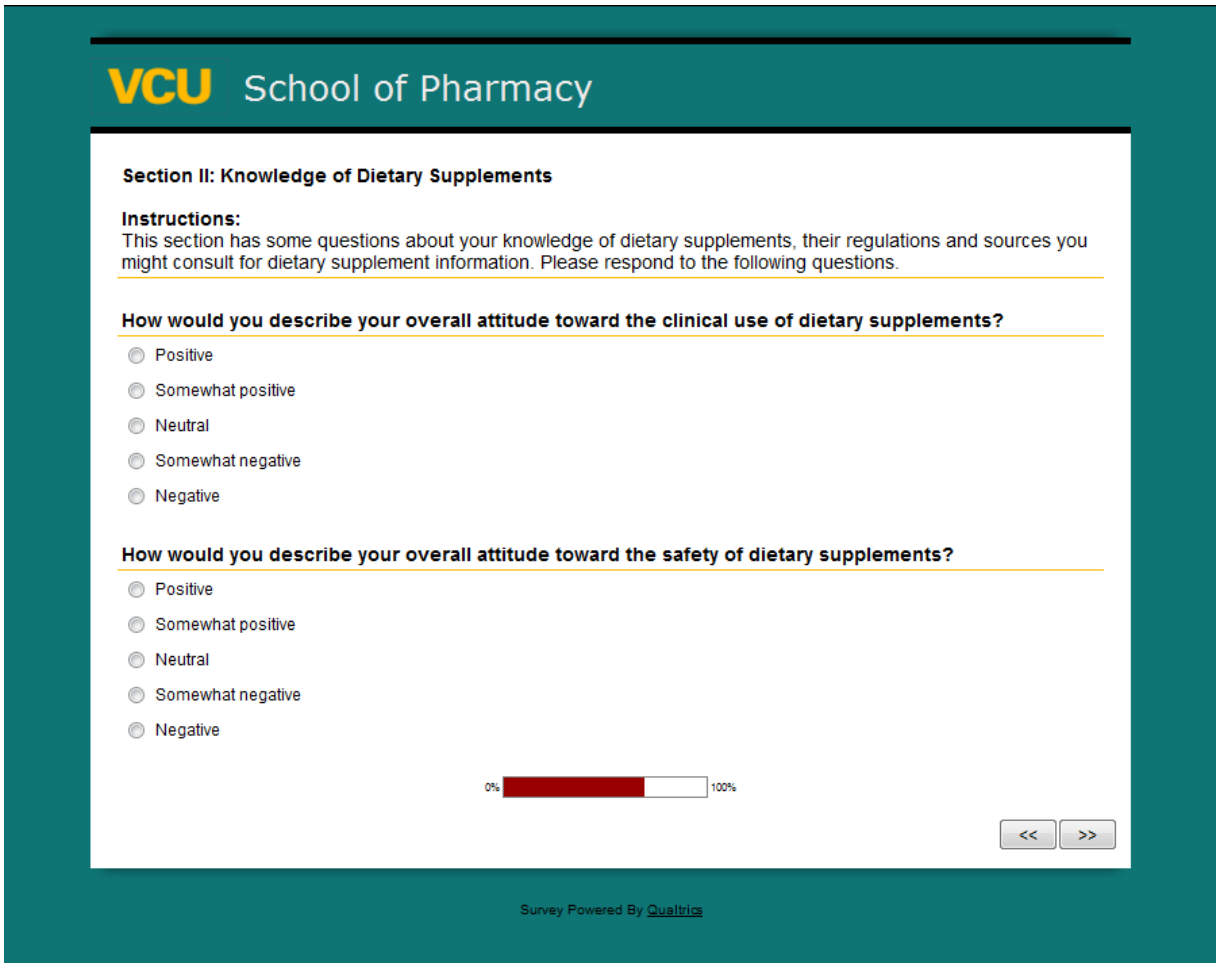


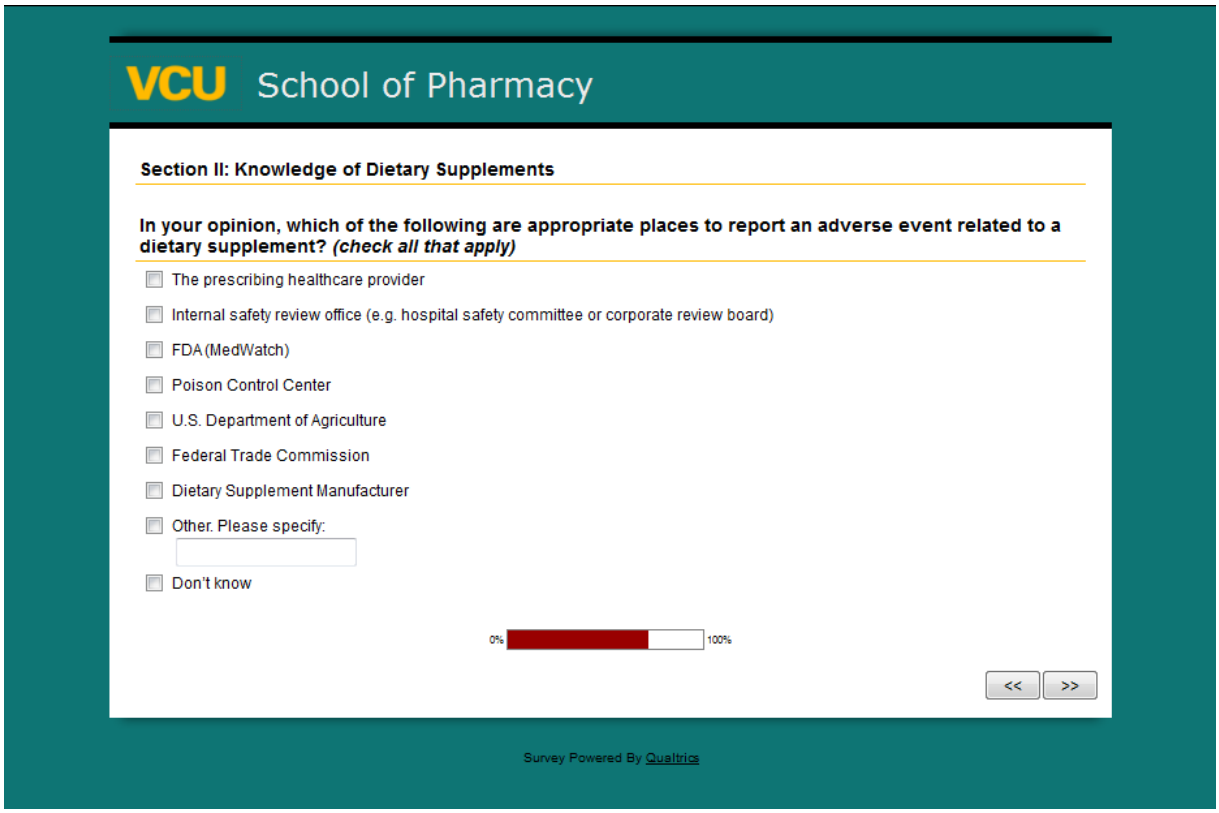


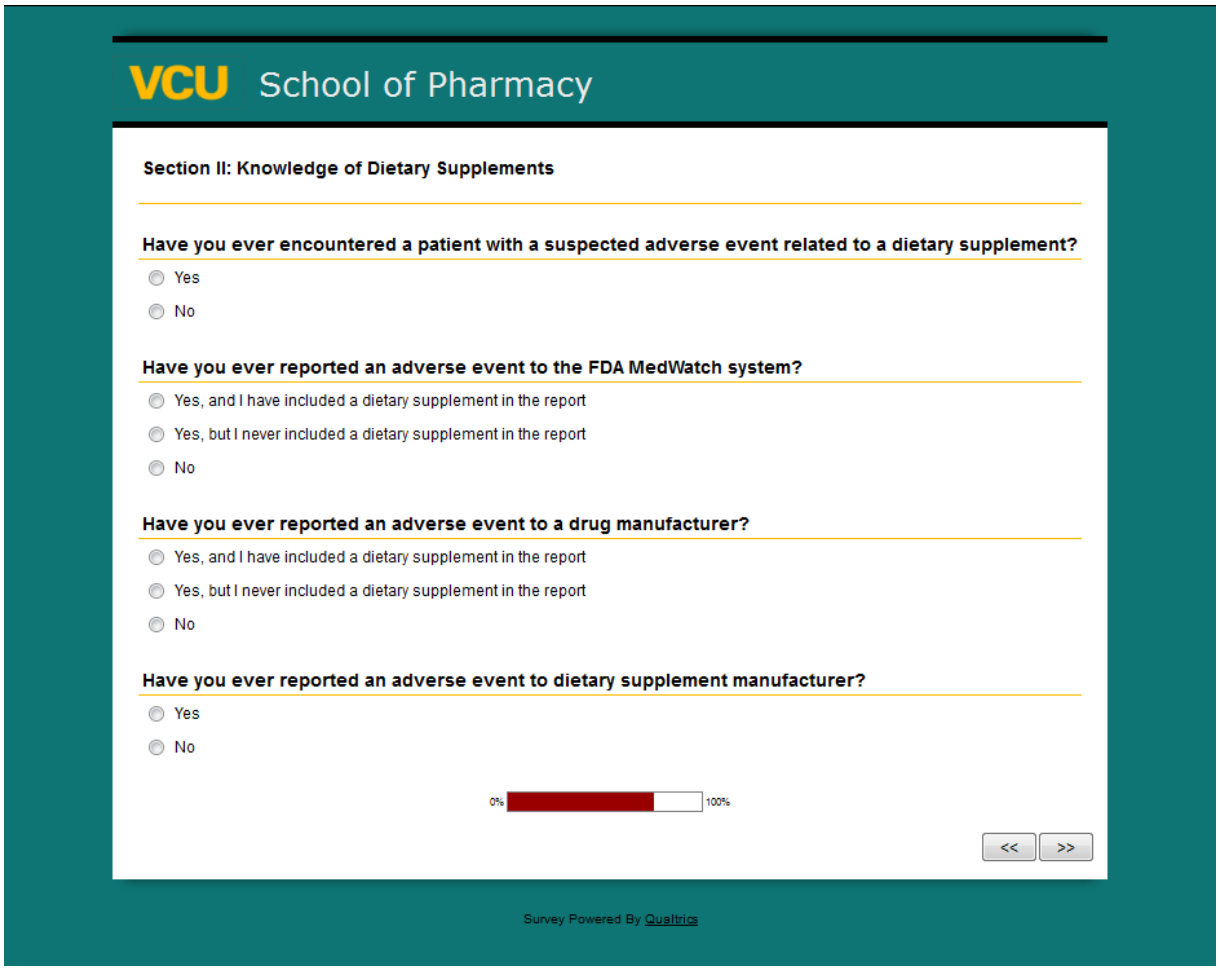


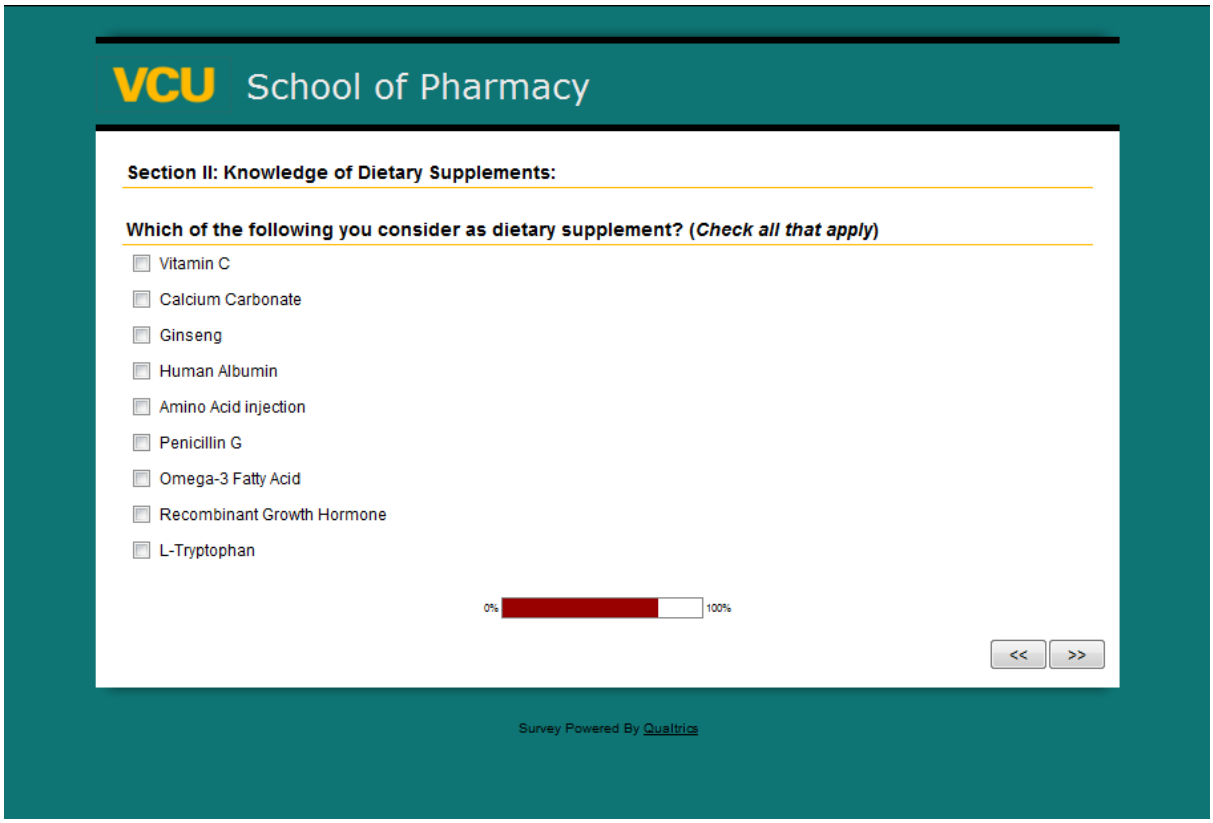


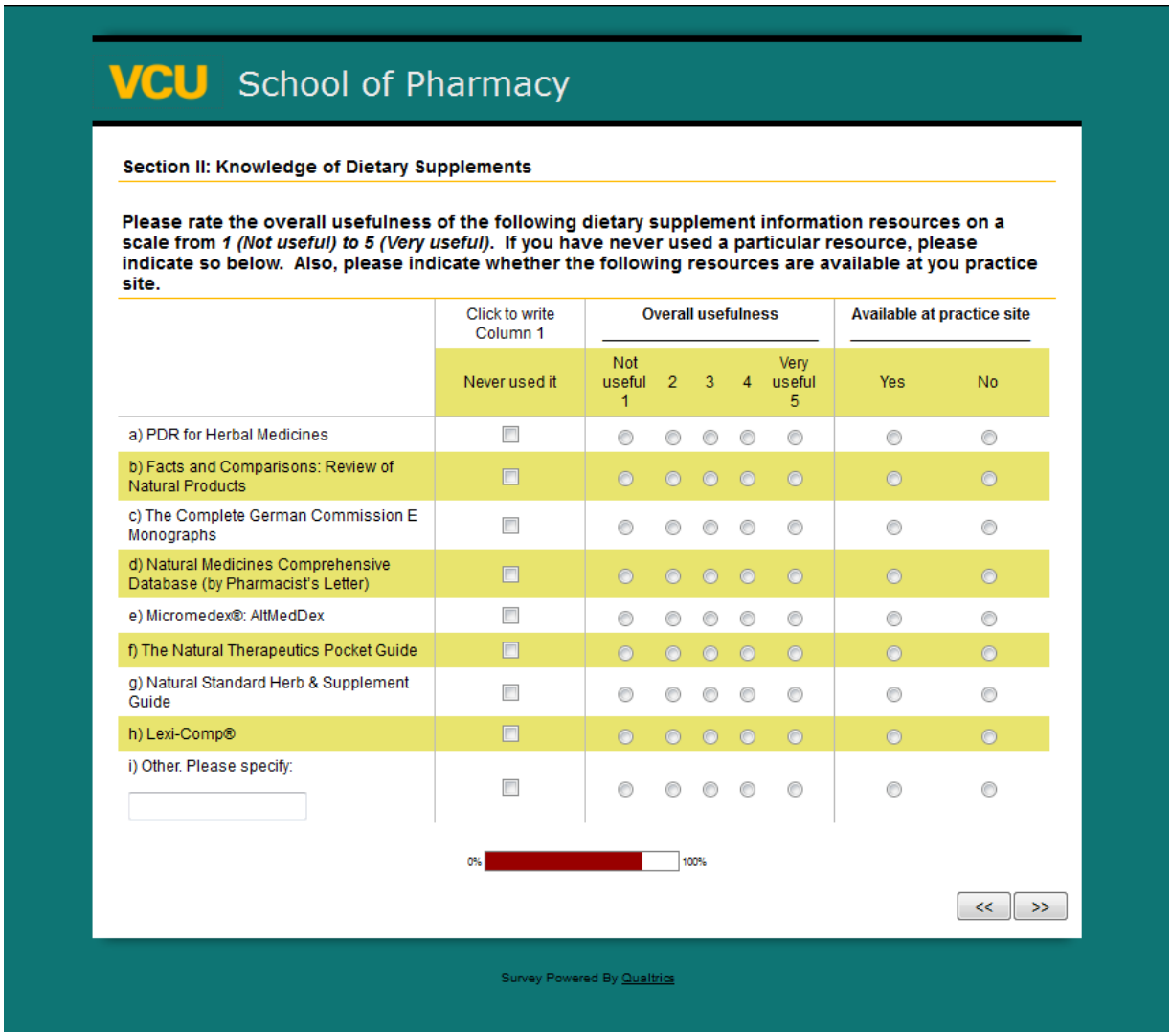












VCU School of Pharmacy

Section II: Knowledge of Dietary Supplements

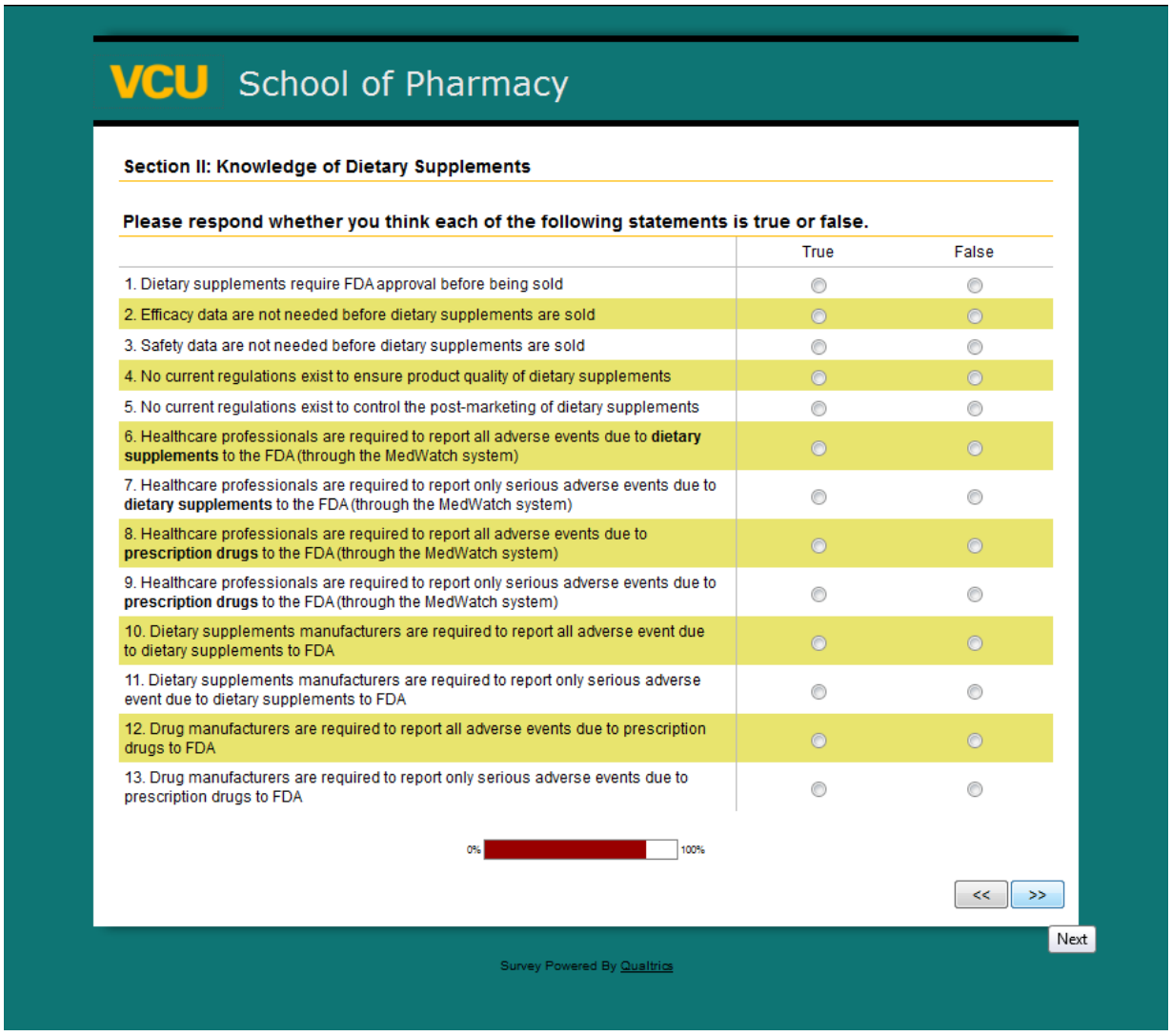
Please rate the overall usefulness of the following dietary supplement information resources on a scale from *1 (Not useful) to 5 (Very useful)*. If you have never used a particular resource, please indicate so below. Also, please indicate whether the following resources are available at you practice site.

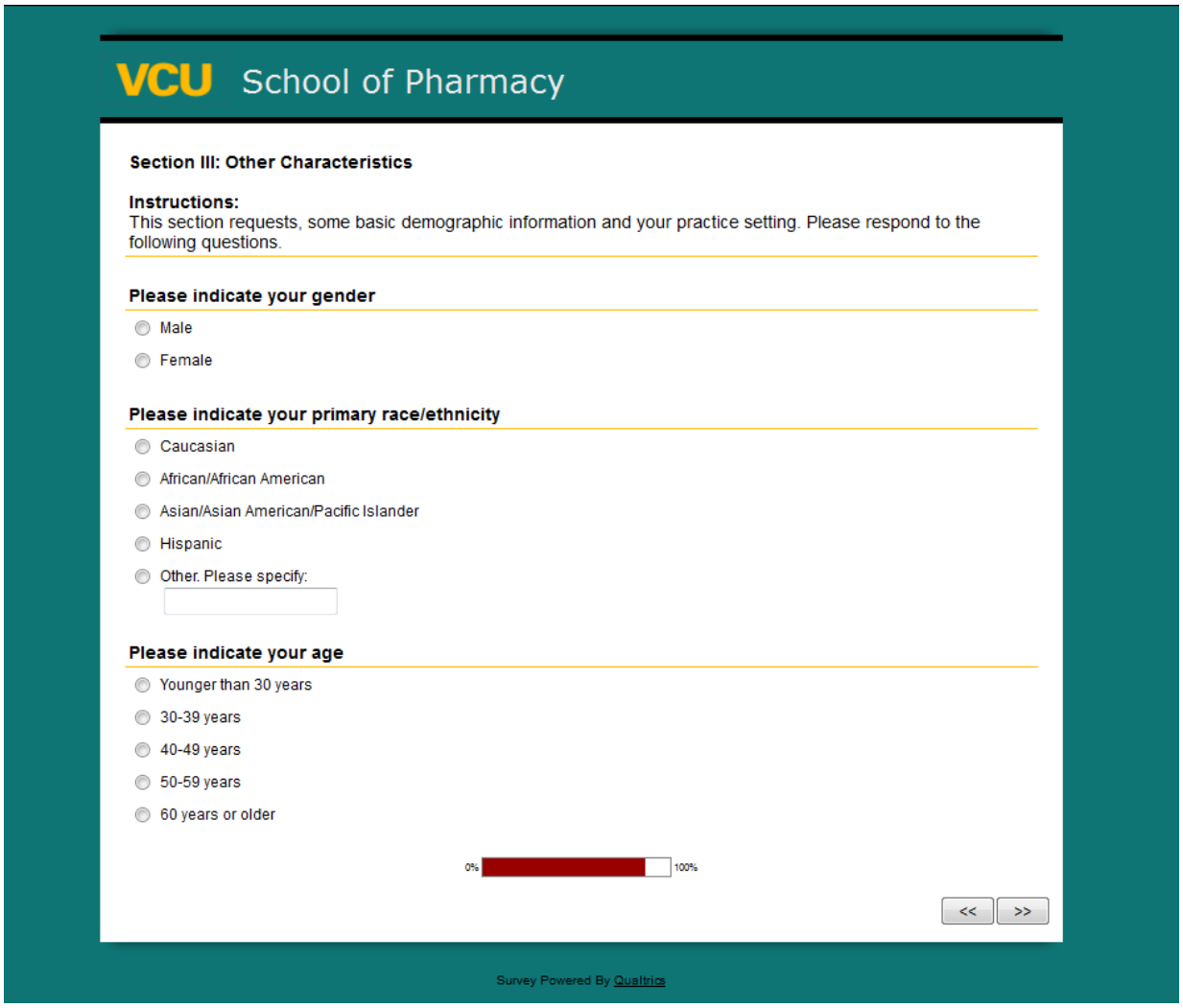
	Click to write Column 1	Overall usefulness					Available at practice site	
	Never used it	Not useful 1	2	3	4	Very useful 5	Yes	No
a) PDR for Herbal Medicines	☐	○	○	○	○	○	○	○
b) Facts and Comparisons: Review of Natural Products	☐	○	○	○	○	○	○	○
c) The Complete German Commission E Monographs	☐	○	○	○	○	○	○	○
d) Natural Medicines Comprehensive Database (by Pharmacist's Letter)	☐	○	○	○	○	○	○	○
e) Micromedex®: AltMedDex	☐	○	○	○	○	○	○	○
f) The Natural Therapeutics Pocket Guide	☐	○	○	○	○	○	○	○
g) Natural Standard Herb & Supplement Guide	☐	○	○	○	○	○	○	○
h) Lexi-Comp®	☐	○	○	○	○	○	○	○
i) Other. Please specify:	☐	○	○	○	○	○	○	○

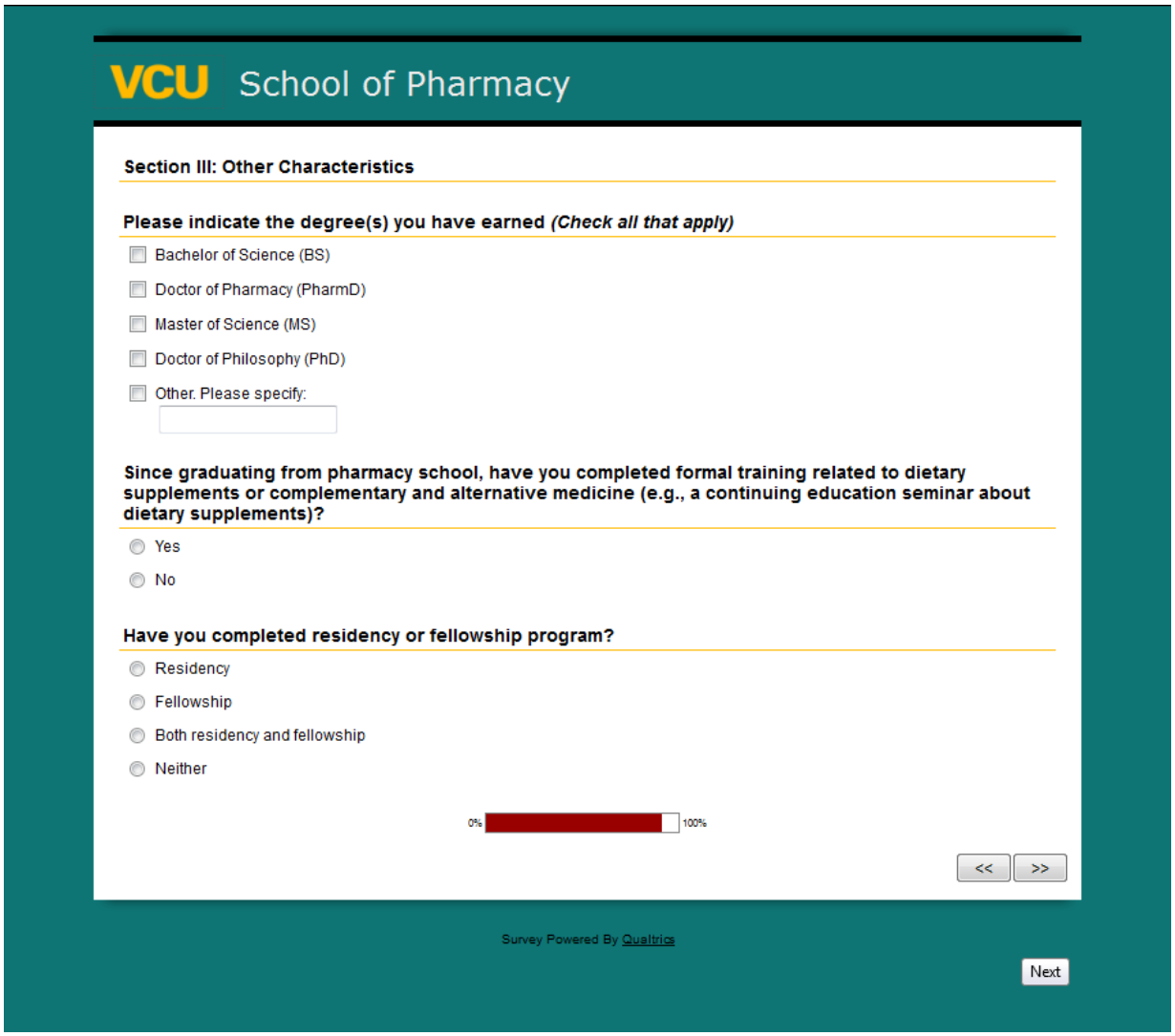
0% 100%

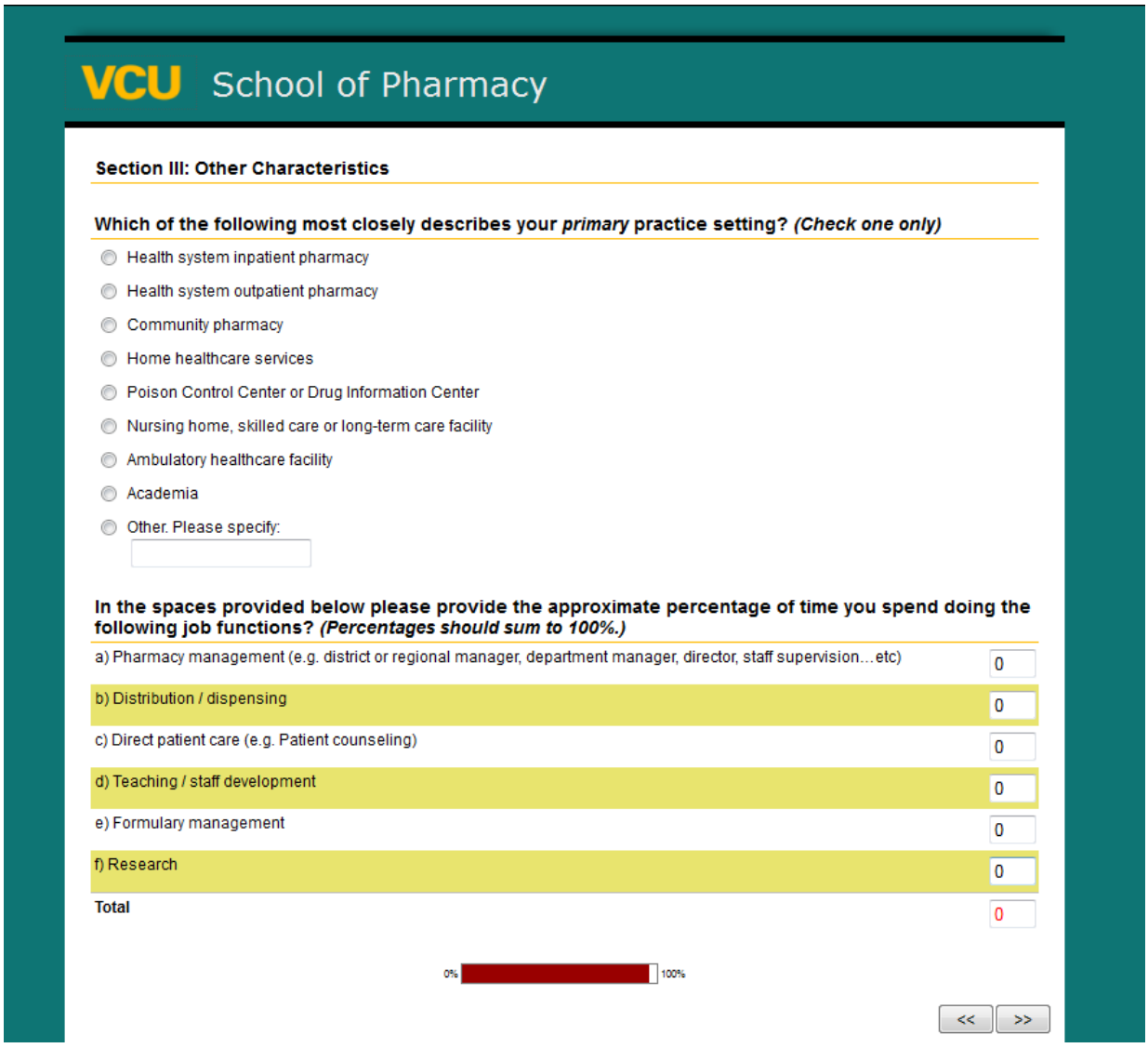
<< >>

Survey Powered By Qualtrics









APPENDIX D

Participant Recruitment E-Mail Template

Dear participant,

My name is Ali Al-hammad. Currently, I am a PhD student at the VCU School of Pharmacy where I am focusing on drug safety issues. One of my particular interests is in the safe use of complementary and alternative therapies, such as natural products and dietary supplements. My dissertation project is focused on examining the factors that influence whether pharmacists report adverse events associated with the use of dietary supplements. Identifying these factors may help in developing educational programs to improve the awareness of pharmacists and other healthcare professionals about dietary supplements and the need for systematic safety surveillance.

I have chosen to use pharmacists who have served as preceptors for VCU pharmacy students. Below is a link to an online survey. It should take about 15 minutes to complete. All of your responses will be anonymous, and your participation is completely voluntary. More information about the project and the survey itself can be found by following the link.
http://vcupharmacy.us2.qualtrics.com/SE/?SID=SV_bloYvnmMf3q4tPS

Your participation would greatly help me complete my dissertation project. If you have any questions, please feel free to e-mail me or my advisor, Dr. Spencer Harpe (seharpe@vcu.edu).

Thank you in advance for helping me with my research project.

Best,

Ali Al-hammad

APPENDIX E

Thank You/Reminder E-Mails

First "Thank You/Reminder" E-mail

Dear participant,

About one week ago, you should have received from me an e-mail that contained a link to an online survey to help me complete my dissertation research project. As a brief reminder, my dissertation project is focused on examining the factors that influence whether pharmacists report adverse events associated with the use of dietary supplements. Identifying these factors may help in developing educational programs to improve the awareness of pharmacists and other healthcare professionals about dietary supplements and the need for systematic safety surveillance.

If you have already responded to the survey, I sincerely thank you for your participation. You can disregard this e-mail. If you have not yet completed the survey, I would greatly appreciate your taking the time (about 15 minutes) to complete the survey by following the link below. All of your responses will be anonymous, and your participation is completely voluntary.
http://vcupharmacy.us2.qualtrics.com/SE/?SID=SV_bloYvnmMf3q4tPS

Your participation would greatly help me complete my dissertation project. If you have any questions, please feel free to e-mail me or my advisor, Dr. Spencer Harpe (seharpe@vcu.edu).

Thank you in advance for helping me with my research project.

Best,

Ali Al-hammad

Second "Thank You/Reminder" E-mail

Dear participant,

About two weeks ago, you should have received from me an e-mail that contained a link to an online survey to help me complete my dissertation research project. As a brief reminder, my dissertation project is focused on examining the factors that influence whether pharmacists report adverse events associated with the use of dietary supplements. Identifying these factors may help in developing educational programs to improve the awareness of pharmacists and other healthcare professionals about dietary supplements and the need for systematic safety surveillance.

If you have already responded to the survey, I sincerely thank you for your participation. You can disregard this e-mail. If you have not yet completed the survey, I would greatly appreciate your taking the time (about 15 minutes) to complete the survey by following the link below. All of your responses will be anonymous, and your participation is completely voluntary.
http://vcupharmacy.us2.qualtrics.com/SE/?SID=SV_bloYvnmMf3q4tPS

Your participation would greatly help me complete my dissertation project. If you have any questions, please feel free to e-mail me or my advisor, Dr. Spencer Harpe (seharpe@vcu.edu).

Thank you in advance for helping me with my research project.

Best,

Ali Al-hammad

Third "Thank You/Reminder" E-mail

Dear participant,

About two weeks ago, you should have received from me an e-mail that contained a link to an online survey to help me complete my dissertation research project. As a brief reminder, my dissertation project is focused on examining the factors that influence whether pharmacists report adverse events associated with the use of dietary supplements. Identifying these factors may help in developing educational programs to improve the awareness of pharmacists and other healthcare professionals about dietary supplements and the need for systematic safety surveillance.

If you have already responded to the survey, I sincerely thank you for your participation. You can disregard this e-mail. If you have not yet completed the survey, I would greatly appreciate your taking the time (about 15 minutes) to complete the survey by following the link below. All of your responses will be anonymous, and your participation is completely voluntary.
http://vcupharmacy.us2.qualtrics.com/SE/?SID=SV_bloYvnmMf3q4tPS

Your participation would greatly help me complete my dissertation project. If you have any questions, please feel free to e-mail me or my advisor, Dr. Spencer Harpe (seharpe@vcu.edu).

Thank you in advance for helping me with my research project.

Best,

Ali Al-hammad

Final "Thank You" E-mail

Dear participant,

I sincerely thank you for assisting me with my dissertation research. Your participation would greatly help me complete my dissertation project.
If you have any questions, please feel free to e-mail me or my advisor, Dr. Spencer Harpe (seharpe@vcu.edu).

All of your responses will be anonymous, and your participation is completely voluntary.

Best,

Ali Al-hammad

APPENDIX F

Detailed Results

Table F.1 – Relationship between respondent characteristics and the overall attitudes toward the clinical use of DS

		Overall Attitude (%)					
	Categories	**Positive**	**Somewhat positive**	**Neutral**	**Somewhat negative**	**Negative**	**p-value**
Gender n=202							0.515
	Male	8.22%	31.51%	23.29%	26.03%	10.96%	
	Female	8.53%	33.33%	28.68%	24.81%	4.65%	
Age categories n=203							0.519
	Younger than 30 years	8.09%	16.04%	32.32%	40.05%	4.10%	
	30-39 years	3.57%	33.93%	26.79%	30.36%	5.36%	
	40-49 years	9.09%	34.55%	27.27%	21.82%	7.27%	
	50-59 years	13.46%	36.54%	21.15%	23.08%	5.77%	
	60 years or older	6.67%	26.67%	33.33%	13.33%	20.00%	
Race/ Ethnicity n=200*							0.375
	Caucasian	8.38%	32.34%	24.55%	26.35%	8.38%	
	Asian/Asian American/ Pacific Islander	0.00%	25.00%	40.00%	35.00%	0.00%	
	Other	15.38%	38.46%	30.77%	15.38%	0.00%	
Formal training related to DS or CAM n=204							**0.001**
	Yes	21.43%	45.24%	11.90%	14.29%	7.14%	
	No	5.56%	28.40%	30.25%	29.01%	6.79%	

DS: dietary supplement; CAM: complementary and alternative medicine
* The African American category was merged with the *Other* category because of low sample size

Table F.2 – Relationship between respondent characteristics and the overall attitudes toward the safety of DS

		Overall Attitude (%)					
	Categories	Positive	Somewhat positive	Neutral	Somewhat negative	Negative	p-value
Gender n=202							0.438
	Male	1.37%	27.40%	28.77%	31.51%	10.96%	
	Female	3.88%	20.16%	36.43%	32.56%	6.98%	
Age categories n=203							0.638
	Younger than 30 years	0.00%	16.00%	36.00%	40.00%	8.00%	
	30-39 years	1.79%	23.21%	25.00%	39.29%	10.71%	
	40-49 years	1.82%	25.45%	32.73%	32.73%	7.27%	
	50-59 years	7.69%	23.08%	34.62%	25.00%	9.62%	
	60 years or older	0.00%	20.00%	53.33%	26.67%	0.00%	
Race/ Ethnicity* n=200							0.080
	Caucasian	3.59%	20.96%	32.34%	33.53%	9.58%	
	Asian/Asian American/ Pacific Islander	0.00%	20.00%	25.00%	55.00%	0.00%	
	Other	0.00%	38.46%	53.85%	0.00%	7.69%	
Formal training related to DS or CAM n=204							0.132
	Yes	7.14%	30.95%	33.33%	26.19%	2.38%	
	No	2.47%	19.75%	32.72%	35.19%	9.88%	

DS: dietary supplement; CAM: complementary and alternative medicine
* African American category was merged with Other category because of low sample size

Table F.3 – Raw distribution of the overall attitudes toward the clinical use of DS by race and formal training related to DS

		Overall Attitude Toward (%)				
	Categories	Positive	Somewhat positive	Neutral	Somewhat negative	Negative
Race/ Ethnicity*	Caucasian	3.6%	21.0%	32.3%	33.5%	9.6%
	Asian/Asian American/ Pacific Islander	0.0%	20.0%	25.0%	55.0%	0.0%
	Other	0.0%	38.5%	53.8%	0.0%	7.7%
Formal training related to DS or CAM	Yes	7.1%	31.0%	33.3%	26.2%	2.4%
	No	2.5%	19.8%	32.7%	35.2%	9.9%

DS: dietary supplement; CAM: complementary and alternative medicine
* African American category was merged with Other category because of low sample size

Table F.4 – Raw distribution of the overall attitudes toward the safety of DS by race and formal training related to DS

		Overall Attitude Toward (%)				
	Categories	Positive	Somewhat positive	Neutral	Somewhat negative	Negative
Race/ Ethnicity*	Caucasian	3.6%	21.0%	32.3%	33.5%	9.6%
	Asian/Asian American/ Pacific Islander	0.0%	20.0%	25.0%	55.0%	0.0%
	Other	0.0%	38.5%	53.8%	0.0%	7.7%
Formal training related to DS or CAM	Yes	7.1%	31.0%	33.3%	26.2%	2.4%
	No	2.5%	19.8%	32.7%	35.2%	9.9%

DS: dietary supplement; CAM: complementary and alternative medicine
* African American category was merged with Other category because of low sample size

Source	SS	df	MS		
Model	656.531774	17	38.6195161	Number of obs =	743
Residual	1729.1479	725	2.38503159	F(17, 725) =	16.19
				Prob > F =	0.0000
Total	2385.67968	742	3.21520172	R-squared =	0.2752
				Adj R-squared =	0.2582
				Root MSE =	1.5444

report1	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_l_45	-.0901126	.0813812	-1.11	0.269	-.2498835	.0696583
_Iage_l_70	.0635705	.081053	0.78	0.433	-.0955561	.2226971
_Iduration__1	.0675923	.0570529	1.18	0.237	-.0444163	.1796008
_Itime_l_1	.0533009	.0579919	0.92	0.358	-.0605513	.1671531
_Ievidence__2	.0970357	.0820167	1.18	0.237	-.0639829	.2580543
_Ievidence__3	-.7681562	.080373	-9.56	0.000	-.9259479	-.6103645
_Ioutcome_l_1	.708289	.1029965	6.88	0.000	.506082	.910496
_Ioutcome_l_2	.0438097	.0993739	0.44	0.659	-.1512852	.2389047
_Ioutcome_l_3	.175543	.0971795	1.81	0.071	-.0152439	.3663298
_Ia2_4_2	.3731772	.1177938	3.17	0.002	.1419195	.6044349
_Ia3_7_2	.6472954	.2582186	2.51	0.012	.14035	1.154241
a2_2	.2829199	.0802503	3.53	0.000	.1253691	.4404707
_Ia3_2_2	.7319205	.2666606	2.74	0.006	.2084014	1.25544
_Ia2_5_3	-.2848436	.1189597	-2.39	0.017	-.5183902	-.0512969
a2_1	-.3257765	.073081	-4.46	0.000	-.4692521	-.1823008
_Ia3_6_4	-.2817904	.1261372	-2.23	0.026	-.5294283	-.0341525
_Ia3_7_7	.7005898	.3010481	2.33	0.020	.1095597	1.29162
_cons	4.445264	.261511	17.00	0.000	3.931855	4.958673

Figure F.1 – Backward stepwise selection of significant all two way interactions and covariates at alpha=0.05 for reporting to prescriber

Source	SS	df	MS		
Model	687.522048	20	34.3761024	Number of obs =	743
Residual	1785.36893	722	2.47281016	F(20, 722) =	13.90
				Prob > F =	0.0000
Total	2472.89098	742	3.33273717	R-squared =	0.2780
				Adj R-squared =	0.2580
				Root MSE =	1.5725

report2	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_l_45	-.0909727	.0829363	-1.10	0.273	-.2537978	.0718524
_Iage_l_70	.0794993	.0827016	0.96	0.337	-.0828651	.2418637
_Iduration__1	.1406588	.0580666	2.42	0.016	.0266592	.2546584
_Itime_l_1	.0696777	.0589612	1.18	0.238	-.0460781	.1854336
_Ievidence__2	.1354989	.0839121	1.61	0.107	-.029242	.3002398
_Ievidence__3	-.503152	.0820423	-6.13	0.000	-.664222	-.3420819
_Ioutcome_l_1	.9801716	.1047743	9.36	0.000	.7744729	1.18587
_Ioutcome_l_2	-.1407437	.1016334	-1.38	0.167	-.340276	.0587887
_Ioutcome_l_3	.051685	.0991174	0.52	0.602	-.1429077	.2462778
_Ia3_7_3	-.3561325	.1429939	-2.49	0.013	-.636866	-.0753989
a2_1	-.3193013	.0748661	-4.26	0.000	-.4662825	-.17232
_Ia2_4_2	.4303805	.1278653	3.37	0.001	.1793482	.6814128
_Ia2_6_2	-.4789603	.2427553	-1.97	0.049	-.9555509	-.0023697
a2_2	.197362	.0836322	2.36	0.019	.0331707	.3615532
_Ia3_7_8	-.5898756	.295519	-2.00	0.046	-1.170055	-.0096964
_Ia3_2_5	-1.185343	.5725435	-2.07	0.039	-2.309392	-.0612939
_Ia3_7_7	.926378	.3085697	3.00	0.003	.3205768	1.532179
_Ia3_2_2	.6879921	.2704194	2.54	0.011	.1570898	1.218894
_Ia2_6_3	-.6507519	.2482497	-2.62	0.009	-1.138129	-.1633744
_Ia2_7_2	-.8453017	.3188868	-2.65	0.008	-1.471358	-.2192455
_cons	4.441455	.3317903	13.39	0.000	3.790066	5.092844

Figure F.2 – Backward stepwise selection of significant all two way interactions and covariates at alpha=0.05 for reporting to the drug manufacturer

Source	SS	df	MS		
Model	542.165244	17	31.8920732	Number of obs =	743
Residual	1721.07567	725	2.37389748	F(17, 725) =	13.43
				Prob > F =	0.0000
Total	2263.24092	742	3.05018991	R-squared =	0.2396
				Adj R-squared =	0.2217
				Root MSE =	1.5407

report3	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_l_45	-.1368445	.0812928	-1.68	0.093	-.2964418	.0227528
_Iage_l_70	.1289968	.0809887	1.59	0.112	-.0300035	.2879971
_Iduration__1	.0382484	.0568348	0.67	0.501	-.073332	.1498289
_Itime_l_1	.0898029	.0576269	1.56	0.120	-.0233327	.2029384
_Ievidence__2	.0675094	.0825388	0.82	0.414	-.0945343	.2295531
_Ievidence__3	-.408355	.0802433	-5.09	0.000	-.565892	-.250818
_Ioutcome_l_1	.9777807	.1026973	9.52	0.000	.7761612	1.1794
_Ioutcome_l_2	-.2001776	.0991708	-2.02	0.044	-.3948737	-.0054814
_Ioutcome_l_3	-.0428283	.0971126	-0.44	0.659	-.2334839	.1478272
_Ia2_6_3	-.7284599	.2435303	-2.99	0.003	-1.206569	-.2503511
_Ia3_7_7	1.219984	.2994643	4.07	0.000	.6320636	1.807905
_Ia2_7_2	-.7384843	.3094601	-2.39	0.017	-1.346029	-.1309394
_Ia3_2_2	.5397994	.262762	2.05	0.040	.0239341	1.055665
_Ia3_1_2	.2585795	.1218956	2.12	0.034	.0192691	.49789
_Ia3_6_4	.2434671	.1218017	2.00	0.046	.0043409	.4825932
_Ia2_4_2	.533253	.1221102	4.37	0.000	.2935211	.7729848
_Ia2_6_2	-.5410885	.2385455	-2.27	0.024	-1.009411	-.0727661
_cons	3.384227	.2832087	11.95	0.000	2.82822	3.940234

Figure F.3 – Backward stepwise selection of significant all two way interactions and covariates at alpha=0.05 for reporting to the DS manufacturer

Source	SS	df	MS		
Model	877.643335	26	33.7555129	Number of obs =	743
Residual	1837.43876	716	2.56625526	F(26, 716) =	13.15
				Prob > F =	0.0000
Total	2715.0821	742	3.6591403	R-squared =	0.3232
				Adj R-squared =	0.2987
				Root MSE =	1.602

report4	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_Iage_l_45	-.1162604	.0846692	-1.37	0.170	-.28249	.0499692
_Iage_l_70	.1001948	.0844249	1.19	0.236	-.065555	.2659447
_Iduration__1	.1349038	.0593688	2.27	0.023	.018346	.2514615
_Itime_l_1	.0900477	.0610748	1.47	0.141	-.0298594	.2099547
_Ievidence__2	.14916	.0862854	1.73	0.084	-.0202427	.3185627
_Ievidence__3	-.6537279	.0835109	-7.83	0.000	-.8176834	-.4897725
_Ioutcome_l_1	.8937829	.1072264	8.34	0.000	.6832671	1.104299
_Ioutcome_l_2	-.1454439	.1037584	-1.40	0.161	-.3491509	.0582632
_Ioutcome_l_3	.1571245	.1015587	1.55	0.122	-.042264	.3565131
_Iag45Xdu1	-.1967567	.0731006	-2.69	0.007	-.3402737	-.0532396
_Ia3_3_4	.6981578	.2296574	3.04	0.002	.2472753	1.14904
_Ia3_2_2	.6609727	.2786717	2.37	0.018	.1138614	1.208084
_Ia2_6_2	-.6840203	.2377607	-2.88	0.004	-1.150812	-.2172288
_Ia3_7_8	.6982876	.3090294	2.26	0.024	.0915756	1.305
a2_2	.1947357	.0859074	2.27	0.024	.0260752	.3633962
a2_1	-.2222856	.0773036	-2.88	0.004	-.3740544	-.0705168
_Ia3_2_5	-2.088081	.5942135	-3.51	0.000	-3.25469	-.921472
_Ia3_1_2	.4275834	.135291	3.16	0.002	.1619689	.6931979
_Ia3_3_5	1.049934	.2948636	3.56	0.000	.4710333	1.628835
_Ia3_7_3	-.5970156	.1549188	-3.85	0.000	-.901165	-.2928663
_Ia3_3_2	.6249587	.208519	3.00	0.003	.2155769	1.034341
_Ia3_3_3	.5754473	.216288	2.66	0.008	.1508128	1.000082
_Ia2_4_2	.346026	.1299683	2.66	0.008	.0908615	.6011906
_Ia2_6_3	-.7922123	.2318642	-3.42	0.001	-1.247427	-.3369974
_Ia3_7_7	.7715994	.3210962	2.40	0.017	.1411968	1.402002
_Ia2_5_2	.4272836	.1403442	3.04	0.002	.1517482	.7028189
_cons	2.822252	.3922896	7.19	0.000	2.052076	3.592427

Figure F.4 – Backward stepwise selection of significant all two way interactions and covariates at alpha=0.05 for reporting to FDA

```
Random-effects GLS regression                   Number of obs      =       754
Group variable: resid                           Number of groups   =       196

R-sq:  within  = 0.3289                         Obs per group: min =         1
       between = 0.2350                                        avg =       3.8
       overall = 0.2703                                        max =         4

                                                Wald chi2(17)      =    322.51
corr(u_i, X)   = 0 (assumed)                    Prob > chi2        =    0.0000
```

report1	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iage_l_45	-.1003045	.0675189	-1.49	0.137	-.2326391	.0320302
_Iage_l_70	.0264978	.0684394	0.39	0.699	-.107641	.1606365
_Iduration__1	.092265	.0476449	1.94	0.053	-.0011172	.1856472
_Itime_l_1	.045715	.0495211	0.92	0.356	-.0513446	.1427746
_Ievidence__2	.12227	.0696066	1.76	0.079	-.0141564	.2586965
_Ievidence__3	-.8152563	.0674813	-12.08	0.000	-.9475173	-.6829953
_Ioutcome_l_1	.5668594	.0880189	6.44	0.000	.3943456	.7393732
_Ioutcome_l_2	.0320458	.083362	0.38	0.701	-.1313407	.1954324
_Ioutcome_l_3	.2068004	.0812624	2.54	0.011	.0475291	.3660717
Ia2_4_2	.2021499	.0875429	2.31	0.021	.030569	.3737308
Ia3_7_2	.6310777	.3838229	1.64	0.100	-.1212013	1.383357
a2_2	.2467928	.1176301	2.10	0.036	.016242	.4773435
Ia3_2_2	.2568697	.1646428	1.56	0.119	-.0658243	.5795637
Ia2_5_3	-.2303414	.1393698	-1.65	0.098	-.5035011	.0428183
a2_1	-.3071474	.1057284	-2.91	0.004	-.5143713	-.0999235
Ia3_6_4	-.1551287	.0959554	-1.62	0.106	-.3431978	.0329405
Ia3_7_7	.7533595	.4365946	1.73	0.084	-.1023503	1.609069
_cons	4.75396	.3537261	13.44	0.000	4.06067	5.447251
sigma_u	.98193388					
sigma_e	1.1840138					
rho	.40750648	(fraction of variance due to u_i)				

Figure F.5 – Final linear regression model with the significant interactions and covariates for reporting to prescriber

```
Random-effects GLS regression                   Number of obs      =       758
Group variable: resid                           Number of groups   =       197

R-sq:  within  = 0.2830                         Obs per group: min =         1
       between = 0.2861                                        avg =       3.8
       overall = 0.2731                                        max =         4

                                                Wald chi2(20)      =    288.10
corr(u_i, X)   = 0 (assumed)                    Prob > chi2        =    0.0000
```

report2	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iage_l_45	-.0785319	.0645129	-1.22	0.223	-.204975	.0479111
_Iage_l_70	.0468321	.0654121	0.72	0.474	-.0813734	.1750375
_Iduration__1	.1461862	.0455905	3.21	0.001	.0568305	.2355418
_Itime_l_1	.0765672	.0473831	1.62	0.106	-.0163019	.1694364
_Ievidence__2	.1147102	.0666064	1.72	0.085	-.0158359	.2452563
_Ievidence__3	-.5141451	.064536	-7.97	0.000	-.6406335	-.3876568
_Ioutcome_l_1	.8493167	.0839423	10.12	0.000	.6847928	1.013841
_Ioutcome_l_2	-.1741489	.0796873	-2.19	0.029	-.3303331	-.0179647
_Ioutcome_l_3	.0957884	.0778254	1.23	0.218	-.0567467	.2483234
Ia3_7_3	-.4093752	.2186452	-1.87	0.061	-.8379118	.0191615
a2_1	-.3100759	.1144795	-2.71	0.007	-.5344515	-.0857002
Ia2_4_2	.2363833	.0967398	2.44	0.015	.0467769	.4259897
Ia2_6_2	-.3204673	.3579933	-0.90	0.371	-1.022121	.3811867
a2_2	.1803343	.1294983	1.39	0.164	-.0734778	.4341463
Ia3_7_8	-.6195219	.4660372	-1.33	0.184	-1.532938	.2938944
Ia3_2_5	-.9345157	.4894942	-1.91	0.056	-1.893907	.0248752
Ia3_7_7	.9640744	.4707258	2.05	0.041	.0414689	1.88668
Ia3_2_2	.789131	.376871	2.09	0.036	.0504774	1.527785
Ia2_6_3	-.5184981	.3655608	-1.42	0.156	-1.234984	.197988
Ia2_7_2	-.4760971	.2437622	-1.95	0.051	-.9538621	.001668
_cons	4.066913	.4736968	8.59	0.000	3.138484	4.995342
sigma_u	1.1056659					
sigma_e	1.1325221					
rho	.48800265	(fraction of variance due to u_i)				

Figure F.6 – Final linear regression model with the significant interactions and covariates for reporting to the drug manufacturer

```
Random-effects GLS regression                   Number of obs      =       746
Group variable: resid                           Number of groups   =       194

R-sq:  within  = 0.2604                         Obs per group: min =         1
       between = 0.2401                                        avg =       3.8
       overall = 0.2331                                        max =         4

                                                Wald chi2(17)      =    245.51
corr(u_i, X)   = 0 (assumed)                    Prob > chi2        =    0.0000
```

report3	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iage_l_45	-.0945177	.0628182	-1.50	0.132	-.2176392	.0286037
_Iage_l_70	.0971452	.0633599	1.53	0.125	-.0270378	.2213282
_Iduration__1	.0552729	.0442507	1.25	0.212	-.0314569	.1420028
_Itime_l_1	.0973126	.0461008	2.11	0.035	.0069567	.1876684
_Ievidence__2	.0224023	.0649385	0.34	0.730	-.1048748	.1496794
_Ievidence__3	-.4323175	.0628147	-6.88	0.000	-.5554321	-.309203
_Ioutcome_l_1	.8238365	.0815317	10.10	0.000	.6640373	.9836357
_Ioutcome_l_2	-.2053937	.0776449	-2.65	0.008	-.3575748	-.0532125
_Ioutcome_l_3	.0398562	.0755327	0.53	0.598	-.1081852	.1878976
Ia2_6_3	-.5030939	.3565664	-1.41	0.158	-1.201951	.1957633
Ia3_7_7	1.278657	.4603846	2.78	0.005	.37632	2.180995
Ia2_7_2	-.4698438	.2346697	-2.00	0.045	-.9297879	-.0098997
Ia3_2_2	.1741797	.1691147	1.03	0.303	-.157279	.5056383
Ia3_1_2	.1295388	.0950193	1.36	0.173	-.0566957	.3157732
Ia3_6_4	.1272357	.0990275	1.28	0.199	-.0668546	.321326
Ia2_4_2	.279204	.0946724	2.95	0.003	.0936494	.4647586
Ia2_6_2	-.3370879	.35071	-0.96	0.336	-1.024467	.350291
_cons	3.576257	.318172	11.24	0.000	2.952651	4.199863
sigma_u	1.0935236					
sigma_e	1.0899349					
rho	.50164361	(fraction of variance due to u_i)				

Figure F.7 – Final linear regression model with the significant interactions and covariates for reporting to the DS manufacturer

```
Random-effects GLS regression                   Number of obs      =       750
Group variable: resid                           Number of groups   =       195

R-sq:  within  = 0.3360                         Obs per group: min =         1
       between = 0.3281                                        avg =       3.8
       overall = 0.3175                                        max =         4

                                                Wald chi2(26)      =    358.40
corr(u_i, X)   = 0 (assumed)                    Prob > chi2        =    0.0000
```

report4	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iage_l_45	-.068261	.066248	-1.03	0.303	-.1981048	.0615827
_Iage_l_70	.0315542	.0668494	0.47	0.637	-.0994681	.1625765
_Iduration__1	.1290092	.0467972	2.76	0.006	.0372884	.22073
_Itime_l_1	.0996133	.0490597	2.03	0.042	.003458	.1957686
_Ievidence__2	.0856492	.0685186	1.25	0.211	-.0486448	.2199432
_Ievidence__3	-.6358922	.0662324	-9.60	0.000	-.7657054	-.5060791
_Ioutcome_l_1	.8306661	.0858319	9.68	0.000	.6624387	.9988935
_Ioutcome_l_2	-.1825599	.0819621	-2.23	0.026	-.3432027	-.0219172
_Ioutcome_l_3	.1961412	.0799179	2.45	0.014	.039505	.3527774
Iag45Xdu1	-.129076	.0589242	-2.19	0.028	-.2445653	-.0135866
Ia3_3_4	.1357613	.1986269	0.68	0.494	-.2535403	.5250629
Ia3_2_2	1.016255	.390073	2.61	0.009	.2517264	1.780785
Ia2_6_2	-.5737888	.3632149	-1.58	0.114	-1.285677	.1380993
Ia3_7_8	.7567094	.4921475	1.54	0.124	-.207882	1.721301
a2_2	.1739574	.1348852	1.29	0.197	-.0904127	.4383276
a2_1	-.2070594	.1191726	-1.74	0.082	-.4406334	.0265147
Ia3_2_5	-1.154094	.5072475	-2.28	0.023	-2.14828	-.1599067
Ia3_1_2	.2098001	.1047826	2.00	0.045	.0044299	.4151702
Ia3_3_5	.4392696	.2563769	1.71	0.087	-.06322	.9417591
Ia3_7_3	-.5817025	.2405286	-2.42	0.016	-1.05313	-.110275
Ia3_3_2	.0702092	.2414031	0.29	0.771	-.4029321	.5433505
Ia3_3_3	-.0051807	.2443927	-0.02	0.983	-.4841817	.4738202
Ia2_4_2	.2100788	.0998153	2.10	0.035	.0144444	.4057131
Ia2_6_3	-.6959238	.3527074	-1.97	0.048	-1.387218	-.00463
Ia3_7_7	.8424885	.4972137	1.69	0.090	-.1320325	1.817009
Ia2_5_2	.4175135	.2239319	1.86	0.062	-.0213849	.8564118
_cons	3.55102	.5128052	6.92	0.000	2.545941	4.5561
sigma_u	1.1440455					
sigma_e	1.1560481					
rho	.49478185	(fraction of variance due to u_i)				

Figure F.8 – Final linear regression model with the significant interactions and covariates for reporting to FDA

Vita

Ali Alhammad was born in Hufof, Saudi Arabia. He was raised in Rumilah, Al Hassa in eastern province of Saudi Arabia. He is a Saudi resident currently living in Richmond, Virginia, with his wife, Wasilah Alhashim, his two daughters, Wala and Hawra, and his little boy Hassan.

EDUCATION

May 2009 – Present	Virginia Commonwealth University, School of Pharmacy, Richmond, VA Doctor of Philosophy, Pharmacy Administration, to be awarded August 2012
Jan. 2007 – May 2009	Virginia Commonwealth University, School of Pharmacy, Richmond, VA Masters of Sciences, Pharmacy Administration
April 2006 – Dec. 2007	Virginia Commonwealth University, English Language Program, Richmond, VA. ESL certificate
Aug. 2000 – Dec. 2000	King Fahad Military Medical Complex (KFMMC), Dhahran, Kingdom of Saudi Arabia Internship trainee
May 2000 – Aug. 2000	Saudi ARAMCO Medical Services, Dhahran, Kingdom of Saudi Arabia Summer trainee
May 1999 – Aug. 1999	Saudi ARAMCO Medical Services, Dhahran, Kingdom of Saudi Arabia

	Summer trainee
Aug. 1996 – Aug. 2000	King Saud University, School of Pharmacy, Riyadh, Kingdom of Saudi Arabia Bachelor of Science in Pharmaceutical sciences, awarded January. 2001

PROFESSIONAL EXPERIENCE

June – Aug. 2011	Graduate health economist intern, Abbott Laboratories, Greater Chicago area, IL, U.S.A
Aug. 2003 – March 2006	Grade-I hospital pharmacist, King Fahad Military Medical Complex (KFMMC), Dhahran, Kingdom of Saudi Arabia
April 2001 – Aug. 2003	Grade-II hospital pharmacist, King Fahad Military Medical Complex (KFMMC), Dhahran, Kingdom of Saudi Arabia