The Intersection Between Mandatory Adverse Event Reporting and Best Practices for Dietary Supplement Post-market Surveillance

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I receive many opportunities to visit with managers within dietary supplement companies in various stages of understanding the importance of product safety surveillance. Surprisingly, a number of companies are still struggling with the concept of dietary supplement safety, citing the inherently wide margin of safety for most of the natural ingredients that go into finished products today. With the FDA's promulgation of rules and regulations for Good Manufacturing Practices (GMPs), many of those in R&D assume that if they have everything in place for the manufacturing process, safety is a given; while those in the regulatory ranks recognize the need for meeting other regulations aimed at ensuring supplement safety.

One example relates to monitoring and reporting any allegations of Serious Adverse Events (SAE's) to the FDA. Even when companies appear to be on top of watching for allegations of "serious" adverse effects, they sometimes confuse the prescriptive process of meeting their regulatory obligations with the performance-based process of completing post-market surveillance. The differences can distinguish the best practice company from others that may not be meeting the expectations of their customers, suppliers, retailers, regulators and even their insurance carrier. Just as important, they may not be protecting their company, their brand, and the future viability of their products.

Next, the inherently wide margin of safety associated with the majority of dietary supplement ingredients often gets in the way of companies inputting robust systems for safety surveillance. Often times when I ask a company executive if they receive reports of adverse effects from their consumers, they say they rarely hear of anybody experiencing an adverse effect with their product. They go on to say that occasionally somebody will report that the product caused or contributed to some unusual and potentially serious health malady but they are quick to let the consumer know that their product "doesn't cause that type of reaction." When asked to describe their adverse event reporting system, it's not unusual to learn they have no formal surveillance system in place to document an event. These manager responses range from those with credible, high-end surveillance systems, to those with nonexistent ones.

There are many companies who do a great job of documenting and reporting their SAE's; however, with the FDA recently citing statistics from their enforcement division that up to 70% of dietary supplement companies have GMP deficiencies, along with concerns about underreporting of AE's, it's time for supplement manufacturer management to review their internal process and why it's important to the product life cycle.

Regulatory Framework for Ensuring Safety

When thinking about post-market surveillance for supplement safety, one might first want to review the FDA's regulatory authority to ensure such safety. Despite passage of the adverse event regulations in 2006, the FDA had previously been granted substantial regulatory authority over dietary supplements related to safety, which were further enhanced and expanded by the Dietary Supplement Health and Education Act (DSHEA). DSHEA did not change any existing FD&C regulations that specifically prohibited any poisonous or deleterious substances in dietary supplements. Rather, DSHEA maintained the rules prohibiting significant or unreasonable risk of injury that allows the FDA the authority to issue immediate bans related to imminent hazards and also establish good manufacturing practices.

Included in the GMP rules and regulations were specific provisions for documenting and reporting adverse events related to manufacturing issues. In addition to regulatory options for the FDA to identify unsafe products and take action to remove them, the FDA enforces mandatory adverse event reporting requirements for dietary supplements manufacturers, and monitors other requirements of the Dietary Supplement and Nonprescription Drug Consumer Protection Act, including record keeping, data archiving, establishment of policies and procedures related to adverse event management and documentation, and the timely submissions of required adverse events directly to the Agency.

It would seem that if the manufacturer met their GMP obligations and reported allegations of serious adverse events to the FDA, there wouldn't be much left to do. However, simply meeting the letter of the law is not going to protect any manufacturer from product liability should the product actually cause unintended adverse effects. Even if the manufacturer has not violated any rules or regulations, the damage to the company and its brand can be significant and costly if the product potentially causes consumer injury. Many of the most adverse event related issues that have occurred within the dietary supplement market have had nothing to do with an appropriately formulated and manufactured product.

Take, for example, the Total Body Health liquid multivitamin product involved in a manufacturing breach in 2008. This GMP breach resulted in massive amounts of selenium being mistakenly added to the product. The manufacturer was ill equipped to identify and manage the issue when consumers tried to report their adverse event experiences to the manufacturer's non-existent surveillance system. Without the help of the manufacturer, it took a number of weeks for poison control centers and multiple regulatory authorities to piece together the connection between product use and reported adverse effects.

Thinking Post-market Surveillance

Despite significant and comprehensive rules and regulations designed to ensure the safety of dietary supplement ingredients, it's the ongoing monitoring and collection of surveillance data once the product is in commerce that remains the cornerstone of effective safety surveillance. To better understand the kind of data needed to monitor safety, it is imperative to understand the goals of any post-market surveillance initiative, and the events needed to identify, manage, mitigate, and prevent. The first step in establishing a system of surveillance is to define what it should accomplish.

Goals and Objectives of a Best Practice Dietary Supplement Post-market Surveillance (PMS) System:

- Ensure that pre-market assessments or beliefs of inherent safety are realized during consumer use of the product.

- Ensure known safety concerns have been identified and considered, as well as warned of on product labeling.

- Ensure the PMS system is sufficiently "sensitive," such that potential threats or safety concerns would likely be included in the monitored events.

- Ensure the PMS system is sufficiently specific to allow detection, differentiation and ultimately determination of real vs. perceived threats.

- Identify intended and unintended use of patterns which may potentially contribute to "unintended effects."

- Allow assessment of product performance by itself or in the presence of other products or substances.

- Help ensure that effects in unique populations are considered when monitoring safety.

- Further define, document and confirm a relative "safety profile" for the product during real life conditions of use.

To achieve these goals, a combination of both mandatory and best practice post-market surveillance initiatives must be implemented by the manufacturer of dietary supplements. Mandatory serious adverse event reporting must meet the requirements of the *Dietary Supplement and Nonprescription Drug Consumer Protection Act* of 2006. Best practice post-market surveillance initiatives are designed to meet both regulatory requirements and business needs associated with ensuring the product lifecycle in the context of monitoring the customer experience, efficacy, and safety.

Understanding and Meeting Regulatory AE Reporting Obligations

The AE legislation included a number of key features within the listed rules and regulations related to the mandatory reporting of adverse events. First, only "serious" adverse events were included in the mandatory reporting component of the legislation. Although mandatory reporting is limited to serious adverse events, the manufacturer is obligated to document and assess every allegation of an adverse effect associated with a dietary supplement to determine whether or not it meets the “serious” criteria for reporting to the FDA.

It makes no difference whether the manufacturer thinks the AE is causally related to the use of the product. What counts is whether any adverse health-related event was reported in association with the use of a dietary supplement, regardless of whether the product was used properly according to label directions.

Also, manufacturers must keep all records related to any adverse event report it receives for no less than six years, regardless of whether the adverse event was reported to FDA. These records must be readily available for inspection by FDA compliance officers upon request. In order for manufacturers to comply with the rules and regulations related to mandatory adverse event reporting, they must engage in a number of proactive steps to ensure that reported allegations of adverse effects are properly documented and, when appropriate, submitted to the FDA. These steps include:

- Design or implement a database to manage collected reports and ensure all reports are maintained and/or archived for six years.

- Design or adopt appropriate data fields within the database to allow capturing of incident details, coding and categorizing reported events, and consistently identifying severity outcomes that determine potentially FDA reportable events.

- Design an "intake system" either within the company or outsourced to external professionals, and develop policies and procedures for the triage of calls to appropriate designated staff.

- Conduct an organization-wide employee training program regarding adverse event policies and procedures to ensure that any company personnel who may be contacted regarding an adverse event knows how to properly handle all angles.

- Ensure the system be designed to manage and document all incoming incidents from all methods of consumer communication including e-mail, postal mail, phone calls, web-based correspondence, and social media portals.

- Establish internal policies and procedures to ensure all "expedited reports" are submitted to the FDA within the 15 business day reporting period.

Why is Post-market Surveillance Important to the Manufacturer and their Consumers?

Meeting regulatory requirements for reporting of "serious" adverse events to the FDA will ensure a company is not subject to enforcement actions related to under-reporting, albeit will not ensure a product will not be the subject of a safety issue or violation. In fact, safety or quality issues identified by either the FDA or others may lead to further scrutiny of some or all of the events a company may have in its adverse event database. Accordingly, establishing best practices not only to meet regulatory requirements for reporting AE's, but also to meet expectations of overall safety is a critical element of post-market surveillance. The goal of the adverse event surveillance system is to identify intended and unintended product use patterns or conditions that give rise to unintended adverse effects.

Quality Control issues can impact the best of companies by ingredient contamination or GMP breaches during manufacturing. With unusual or uncharacteristic AE reports, the possibility of a counterfeit product with toxic ingredients being substituted for the brand-name product due to financial incentives for counterfeiters could occur. There can also be direct and previously recognized or unrecognized adverse effects associated with a given botanical ingredient, either dose-dependent or dose independent, including idiosyncratic reactions. Long-term effects secondary to chronicity of use may occur, yet not be seen until the product has been used for days, months or years. There may even be instances of intentional product misuse or abuse that can result in serious health effects.

Herb-drug interactions are frequently cited as a potential concern for botanical ingredients in dietary supplements due to the possible combinations of botanicals being administered with other pharmaceutical agents. Other interactions include unintended adverse effects between product use and diseases, foods, environmental toxins, other botanicals or dietary supplements, and new or old consumer products being used at the same time. The absence of reported effects to a sensitive surveillance system can also help confirm or establish a positive safety record.

A manufacturer should engage appropriately trained and experienced personnel in the management and monitoring of the corporate AE experience. Some organizations may employ such internal staff yet seek outside experts to review and/or offer independent assessment to confirm findings. Other organizations may choose to engage outside professionals to perform and/or assist in the entire process, which can add credibility and reduce concerns over internal bias.

Analyzing the AE Experience

The manufacturer should also be familiar with how adverse events will be reported to them. Dietary supplement adverse events are more likely to be reported by consumers directly to the manufacturer compared to drug adverse effects routinely reported by healthcare professionals. This reporting bias requires manufacturers to implement additional processes for identifying those adverse effects which may represent a potential safety concern from those having nothing to do with the use of the product. Those unrelated events are sometimes referred to as "background noise," loosely defined as alternative causes, reasons, concomitant medical conditions/illnesses or other contributing factors unrelated to product use.

Experts routinely evaluate and score individual events for the strength of standard factors of association between product use and adverse event. This includes evaluating such factors as expectedness, temporality, biological, pharmacological, or physiological plausibility, de-challenge or re-challenge and consideration of confounding variables.

The only way a company can ensure their system will keep them completely informed is to include these features:

- A consistent and accessible portal for all product users to report their experience and the company to receive reports.

- A team of knowledgeable medical experts familiar with concepts and practices related to spontaneously reported adverse event management including receiving, documenting, categorizing and scoring of individual incidents.

- Consistent documentation of incidents with standardized terms and data fields.

- The ability to complete appropriate follow-up and incident investigation for those incidents most likely to yield actionable intervention or prevention strategies.

Acting on Findings and Connecting the Dots

Although legislation dictates that it is the regulator's responsibility to determine if a product or ingredient is unsafe or poses an unreasonable risk to consumers, it is often the manufacturer who preemptively identifies products with safety or quality issues, taking proactive steps to remove or reformulate the product.

In order for both the regulator and the manufacturer to effectively monitor product-related safety issues, a number of sources of data, in addition to AE reports, must be routinely accessed. These sources include clinical studies, published anecdotal case reports, basic science/toxicology animal data, spontaneous adverse event reports sent directly to the FDA, special reports by medical groups or field professionals, and reports from other governmental entities.

Regulators routinely monitor marketed products to identify signals, sentinel events, supporting research, and other factors suggesting a safety issue exists. Throughout this process the manufacturer may also provide data or other information to support, explain, or refute information that may be signaling a suspected safety issue and its significance. This becomes crucial as regulators often draw conclusions regarding safety related concerns based on small numbers of submitted spontaneously reported events typically limited to allegations of “serious” adverse effects. This becomes an issue when regulators may not be familiar with market penetration, incidence rates, or denominator considerations related to market distribution of a given product. In order for manufacturers to adequately address safety signals identified in one or more of the listed information venues, the FDA will expect the manufacturer do the following:

- Present normalized to sales incidence rates for all allegations of injury broken down by age and outcome.

- Track expected incidence rates to determine an acceptable range for likely events and identify unexplained variations to that range in any given time period.

- Present an up-to-date product/ingredient dossier documenting the known toxicology or pharmacology of the product or its ingredients.

- Identify incidents that may signal a safety issue as well as those reported events that are more likely to be representative of background noise.

- Assist FDA in identifying likely causes for suspected sentinel events or for deviations from expected incidence rates.

- Assess the level of concern for any identified adverse effects and provide an evaluation of the likely adverse health impact to consumers using the product.

Closing Message

As regulators and manufacturers review post-market surveillance data, it is important all stakeholders understand the importance of having a sensitive reporting system that encourages and accommodates all consumers to report any suspected relationship between product use and any unexpected or spontaneously appearing adverse health condition to the manufacturer.

The data should not form the primary basis for determining if a safety issues exists; rather, the nature of data should be used to create or support a safety hypothesis generated or being further investigated in one or more of the remaining data information venues. Manufacturers who implement a full range of safety practices will ensure themselves a long, financially viable product lifecycle.