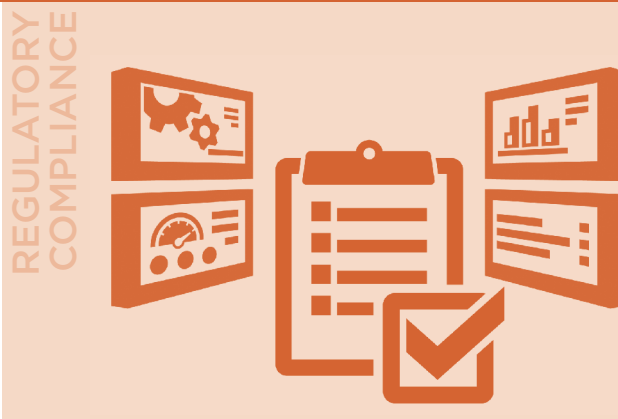


Balancing Pre- and Post-Market Control of Health Supplements

Chan Lai Wah, Benjamin Tan Zhi Yang, Vimal Sachdeva, and Sia Chong Hock



Regulatory authorities (RAs) worldwide employ different terminologies to describe various medicinal and health products. According to the definition by the Association of Southeast Asian Nations (ASEAN), Health supplements (HS) are products used to supplement a diet as well as to maintain and improve the healthy function of human body.¹ They contain one or more active ingredients such as vitamins, minerals, and fatty acids, as well as substances derived from animal, botanical, or synthetic sources. HS are presented in dosage forms such as capsules, tablets, or liquids, but do not include sterile preparations.¹ Similar products are known as food supplements (FS) in the European Union (EU)² and dietary supplements in the United States (US).³ Other terminologies include nutraceuticals, nutritional supplements, natural health products, complementary medicine, health food, and functional food. The products defined by these different terminologies are generally similar but the way they are regulated varies from country to country (Table A).

Currently, the demand for HS is increasing rapidly. Global sales of HS in 2013 was estimated at US\$84.5 billion, a considerable increase from \$62.5 billion in 2008.⁴ Reasons for consumption of HS include seeking improvements in general well-being, “boosting” the immune system, filling perceived nutrient gaps in diets, and improving joint functionality.

The public may have misconceptions that HS are inherently safe on the basis that many active ingredients of HS are derived from natural sources.

Current Problems

Inconsistent quality

Recently, the New York State Attorney General's Office reported that 80% of herbal HS from major global companies tested did not contain any of the herbs listed on the label. Instead, these products contained undeclared fillers such as powdered legumes and wheat.⁵ A review on the quality of HS sold highlighted that the actual content of active ingredients in HS products often did not match the labeled content.⁶ These inconsistencies and quality problems can lead to unintentional overdosing of the active ingredient(s), poisoning, and allergic reactions. Inconsistent quality is due mainly to the HS manufacturer's poor compliance with good manufacturing practices (GMPs) and unethical practices.

Adulteration

A study was conducted on the frequency and characteristics of HS recalls in US from January 2004 to December 2012; active pharmaceutical ingredients (APIs) accounted for all of the 237 HS recalled. Most of the HS recalled were marketed as products for body-building, weight loss, or sexual perfor-

mance.⁷ The unapproved items were usually potent APIs such as sildenafil and corticosteroids, which can cause serious consequences if taken without medical supervision. There were cases in which the consumption of adulterated HS led to severe impairment of vital organs and even death.⁸ Some unscrupulous manufacturers sought to avoid detection of the unauthorized ingredients by using analogues of these compounds or by incorporating these potent unauthorized ingredients in the capsule shells to avoid detection during regulatory or routine quality control tests.⁹

Inappropriate claims

Most HS lack scientific evidence of efficacy. And despite guidelines established by RAs, some companies continue to market their products with inappropriate claims, such as treatment of cancer and prevention of coughs, colds, and flu.¹⁰ Both fly-by-night companies and established companies have engaged in such malpractice. These erroneous claims can pose serious health problems, as they may cause consumers to forgo prescribed medicines in favor of HS with dubious claims of efficacy.

Current Regulatory Controls

Oversight

RAs may implement pre- or postmarket regulatory controls for HS, or enact a combination of both approaches. In premarket regulatory controls, the product is assessed by the RA before it is manufactured or sold. For post-market regulatory controls, the RA may audit HS manufacturers as well as implement product surveillance programs.¹¹ Companies are generally prohibited by most RAs from marketing their HS with medicinal claims to treat, diagnose, or prevent disease.

Harmonization and international collaborations

As mentioned in Table A, each country has its own regulatory requirements for HS. In recent years, several regions and international organizations including ASEAN (section 3.2.2) have begun to harmonize regulatory requirements to facilitate transnational movement of HS across participating countries.

Codex Alimentarius Commission

The Codex Alimentarius Commission (CAC) was established by the World Health Organization (WHO) and the Food and Agriculture Organization to promote harmonization of regulatory requirements for food supplements.²⁰ Like the EU, CAC uses the term “food supplement,” which it defines as a concentrated form of nutrient(s) used to supplement the normal diet, and is presented in dosage forms such as tablets and capsules. It has established guidelines that address the maximum and minimum daily

consumption levels of vitamins and minerals, appropriate claims for such products, packaging, and appropriate choice of vitamins and minerals. The guidelines state that claims of treatment, alleviation, or prevention of disease are prohibited for FS containing vitamins and minerals.

ASEAN

ASEAN is a regional organization that consists of 10 member states: Brunei, Cambodia, Indonesia, Laos, Myanmar, Malaysia, Philippines, Singapore, Thailand, and Vietnam. ASEAN is currently harmonizing HS regulatory requirements to facilitate their transnational movement among member states as part of the integrated ASEAN Economic Community formed on 31 December 2015.²¹ The ASEAN Traditional Medicines and Health Supplements Product Working Group is currently developing an ASEAN regulatory framework, including the harmonization of product technical requirements and GMP compliance. Already harmonized regulatory controls include the list of prohibited active ingredients, maximum limits of vitamins and minerals in HS, labeling requirements, pesticide control, additives and excipients, and the risk of transmissible spongiform encephalopathy.

EU

The EU implemented the Directive 2002/46/EC, approximation of the laws of the member states relating to food supplements, with the goal of facilitating transnational movement of FS among EU Member States.²² Currently, these regulations only apply to FS containing vitamins and minerals. FS containing ingredients other than vitamins and minerals will be regulated by the legislature of individual member states. The FS company has to apply for authorization from European Commission (EC) of the EU if the products contain vitamins or minerals that are not present in the list or if they contain any novel ingredients; these are ingredients that have no history of significant use before 1997. If, however, the company is able to demonstrate that the novel ingredient is significantly equivalent to an existing ingredient, the authorization process can be accelerated.

All FS sold in the EU can only contain claims approved by the EC, and claims relating to disease risk reduction will require higher level of scientific evidence. Companies are also prohibited from marketing their FS with any claims of treating, diagnosing, or preventing diseases.²² Another regulation, Directive 2004/24/EC, covers traditional herbal medicinal products, which in Europe, are generally regulated as medicines.

Effect of differing regulatory frameworks

There is no worldwide agreement on the definition of HS, and the differing regulatory controls across countries have proven to be a challenge for companies marketing their HS globally. As shown in Table A, HS have been regulated as food, medicinal products (MP), or “intermediate” products that straddle both categories. Product categorization helps determine the level of regulatory controls required; regulatory controls for food are usually less demanding than those for MP. The regulatory framework for HS may differ from country to country. For example, Malaysia Drug Control Authority and Health Canada have more stringent regulatory frameworks: Premarket approval is required before sale or manufacture of such products can occur. However, many RAs categorize HS as food products; these HS are regulated under food product laws.

Inconsistent quality is due mainly to poor compliance with GMPs and unethical practices

Some countries such as China and India have yet to establish a legal definition for HS. These countries categorize HS under the broad category of “health food.”²³ Despite the legal definitions of HS in many countries, specific GMP standard for their manufacture have yet to be established. The UK Food Standards Agency, for instance, requires manufacturers to comply with GMP meant for manufacture of food.²⁴

Some countries also have different requirements regarding substantiation of claims used by companies to market HS. For example, the Japanese RA requires clinical trials to be conducted for any claims made by the company before these HS can be marketed. On the other hand, animal tests are sufficient for certain HS claims in China. To further complicate matters, there have been claims for HS that are accepted by EC but rejected by US Food and Drug Administration (FDA).

Recommendations

Premarket ingredient approval

A regulatory framework incorporating a premarket approval process can help avert situations such as the one involving ephedra-containing dietary supplements in the US about 20 years ago. Between 1995 and 1997, US FDA received over 900 reports of adverse events due to ephedra-related toxicity.²⁵ Other botanical ingredients such as kava-kava and yohimbe have been reported to cause liver failure and cardiovascular disorder respectively.²⁴ These adverse events could have been averted with premarket assessments.

Over the years, EU Member States have implemented premarket regulatory controls for HS with the underlying principle that HS must be proven safe for human consumption before they can be sold. On the other hand, some HS companies opine that the EU regulatory system is too stringent and have raised this issue to the European Court of Justice. It was ruled, however, that such a regime is necessary to ensure consumers’ safety. Countries such as Canada and Malaysia have recognized the advantages of pre-market regulatory controls and have adopted similar regulations.

In contrast, premarket regulatory controls for such products are minimal in the US, where the products are presumed to be safe unless proven otherwise with consumers’ access taking center stage.²⁶ There have been counterarguments lamenting the lack of protection of consumers’ safety under the current regulatory framework in the US. In recent years, US FDA has recognized the lack of consumer protection and is reconsidering the current regulatory controls for novel ingredients in such products.²⁷

The premarket approval system adopted by EU is a feasible form of premarket regulatory control to safeguard consumers of HS. RAs could issue a positive list of ingredients that HS are allowed to contain, and companies would be required to submit the composition of the products for approval before they could be sold. If the HS contain active ingredients not present in

Table A: Regulatory controls by agency

Regulatory Agency	Term and definition	Details
China Food and Drug Administration (China FDA) ²	Health food Products meant for providing vitamins and minerals. They are also used for modifying physiological functions. They should not contain any claims of treatment of disease.	<ul style="list-style-type: none"> ■ Products must be registered with China FDA and undergo technical examination by authorized laboratories for safety and efficacy before they can be sold or manufactured in China. ■ China FDA has only approved 27 functional claims, and use of these claims requires validation by animal or human studies or both. ■ The raw materials should conform to the national standards on physical, chemical and microbiological agents. ■ Manufacturers should comply with GMP for health food.
US Food and Drug Administration (US FDA) ³	Dietary supplements Products consumed orally and contain a “dietary ingredient” intended to supplement the diet. The “dietary ingredients” may include vitamins, minerals, botanicals, amino acids, and substances such as enzymes and metabolites.	<ul style="list-style-type: none"> ■ No premarket approval is required. ■ However, if the product contains any new “dietary ingredients”, a premarket notification containing relevant information must be sent to US FDA. ■ Manufacturers must register with US FDA but approval is not required. Manufacturers should comply with GMP for Dietary Supplements established by US FDA. ■ Claims of treating, preventing or diagnosing diseases are prohibited. ■ Premarket approval by US FDA is only required for claims of disease risk reduction. ■ Companies should inform US FDA of any complaints of severe adverse events.
United Kingdom Food Standards Agency (UK FSA) ⁴	Food supplements Products meant to supplement the normal diet; a concentrated source of a vitamin or mineral or other substance with a nutritional or physiological effect, alone or in combination.	<ul style="list-style-type: none"> ■ Only novel products are required to undergo safety assessments; these are products without a significant history of consumption in EU prior to 1997 or produced in a novel manner. ■ The Food Supplements Directive contains the list of permissible vitamins and nutrients that can be present in the product. If the vitamin or nutrient is not listed in the directive, the product cannot be sold. ■ Claims of treatment or prevention of diseases are prohibited. ■ Premarket approval of product claim is done at the EU level.
Singapore Health Sciences Authority (HSA) ⁵	Health supplements Products used to supplement the diet, with benefits beyond those of normal nutrients and/or to support or maintain the healthy functions of the human body.	<ul style="list-style-type: none"> ■ Products must not contain any substances controlled under the Poisons Act. ■ No prior approval required for manufacture and sale of HS. ■ There is no mention of any GMP standard specifically for the manufacture of HS. ■ No premarket approval of claims is required. ■ Products are prohibited from claiming treatment or prevention of diseases.
Australia Therapeutic Goods Administration (TGA) ⁶	Complementary medicine Products consist of one or more designated active ingredients such as vitamins, minerals, herbal materials, etc., and each active ingredient has a clearly established identity and traditional use.	<ul style="list-style-type: none"> ■ Risk-based approach on assessing products. ■ Lower-risk products will be listed on the Australian Register of Therapeutic Goods (ARTG) and evaluated on safety and quality. ■ Higher-risk products should be registered on the ARTG and evaluated for safety, quality and efficacy. ■ If the product contains a novel ingredient, the company must demonstrate its safety during assessment. ■ Australian manufacturers are required to have a license and comply with GMP established by TGA. ■ If the manufacturing process occurs outside of Australia, the company must demonstrate compliance with GMP established by TGA. ■ Listed products are prohibited from containing claims of treatment as well as restricted representations. Registered products are allowed to make restricted representations. Premarket approval is required for restricted representations used by companies to market registered products.
Health Canada (HC) ⁷	Natural health products Products used for: <ol style="list-style-type: none"> a) Diagnosis, treatment or prevention of disease in humans b) Restoring or correcting organic functions in humans c) modifying organic functions in humans to Maintain or promote health 	<ul style="list-style-type: none"> ■ Require a product license. Evidence of product safety and efficacy is required for the application of the license. ■ A site license is required for manufacture and the company needs to demonstrate compliance with Health Canada Guidance for Natural Health Products GMP. ■ Premarket approval of claims is required. Companies that wish to make more serious claims of disease treatment or disease risk reduction are required to provide additional scientific evidence.
Malaysia Drug Control Authority (Malaysia DCA) ⁸	Health supplements Products used to supplement the diet and may contain: <ol style="list-style-type: none"> a) Vitamins, minerals, amino acids, probiotics, and other bioactive substances b) Substances derived from natural sources, including animal, mineral and botanical materials c) Synthetic sources of aforementioned ingredients may only be used if safety has been proven 	<ul style="list-style-type: none"> ■ Require premarket approval. Products have to fulfil safety, quality and appropriateness of claim before it can be approved. ■ Manufacturers have to comply with GMP for HS established by Malaysia DCA in order to obtain the license and product approval. ■ For products that contain disease risk reduction claims, the GMP must be established by Malaysia DCA, PIC/S or RA in the country of manufacture with GMP similar to that of PIC/S. ■ Any claims of treatment, cure or prevention of disease are prohibited. ■ Disease risk reduction claims require human intervention, toxicology and pharmacological studies.
Food Safety and Standards Authority of India (FSSAI) ⁹	Health supplements Products used to satisfy dietary requirements which exist due to a disease or condition. They may contain the following ingredients: <ol style="list-style-type: none"> a) minerals, vitamins, proteins, metals or their compounds, amino acids or enzymes b) botanicals c) substances of animal origin d) a dietary substance used to supplement the diet 	<ul style="list-style-type: none"> ■ Require approval if the products contain any ingredients or additives that are not included in the Rules and Regulations of the Food Safety and Standards Act. ■ Need to obtain manufacturer’s license from FSSAI. ■ Products cannot bear claims of curing or alleviating disease. ■ Products can bear claims of disease risk reduction. ■ Claims must be substantiated with scientific evidence. ■ No GMP established specifically for the manufacture of HS.

Harmonization of HS regulatory requirements could enhance consistency, efficiency, and cost-effectiveness

the list, the ingredients would be subject to safety assessments before the products could be sold. Instead of subjecting every product to individual assessment, premarket approval by ingredients is more practical. Such a regulatory system, based on a positive list of ingredients, would require fewer resources, and would hopefully result in a smaller backlog. In China, where the FDA subjects each product to premarket approval, it is estimated that it can take up to 5 years for a new product to be registered in the country.²³ In comparison, it takes an average of 3 years to approve novel HS ingredients in the EU.

As for HS that contain ingredients that are not in the positive list, approving them on the basis of historical use may be unwise. Historical use may not be a good indicator of safety, as evinced by the adverse events associated with supplements containing kava-kava and ephedra, which have a long history of use as “traditional medicines.”

The US Committee on the Framework for Evaluating the Safety of Dietary Supplements also highlighted that historical use may not always be relevant in assessing the safety of ingredients due to issues such as differences in indications and dosage forms.²⁸ Prohibiting the sale of these products can severely impact consumers who need them. Two possible approaches may be adopted to avoid excessive inconvenience to consumers: The first would require affected companies to engage in safety testing akin to Phase IV clinical trials of new drugs. The companies would be allowed to sell their products while necessary safety tests are being conducted. The products would be withdrawn only when found unsafe. The second approach would allow restricted sale of products to consumers, subject to assessment and verification by physicians, similar to the system for supply of prescription-only medicines. Both approaches, however, would imply that there would still be consumption of products despite the incomplete safety assessment of the ingredients.

As safety is very important, neither approach may be acceptable. To avoid adverse effects, the sale of potentially harmful products should be prohibited during the safety evaluation period. consumer safety should always take precedence over accessibility and business considerations. Moreover, these are not lifesaving products, and the lack of such products is not life-threatening. Therefore, if RAs were to implement a form of premarket framework for HS, the approval of any HS product or ingredient should not be based just on historical use. It has been argued that premarket regulations may reduce consumers’ access to HS by raising economic barriers to market entry. However, it is a minor drawback compared to the risks from the consumption of potentially harmful HS. A premarket regulatory system would also improve the ability of RAs to detect adulterated HS before they are sold, and to deter companies from producing such products.

Premarket claims approval

Inappropriate claims of HS made by companies are a major problem. RAs in countries such as China and Malaysia require companies to submit claims for approval before the HS can be sold; in contrast, this is not required in countries such as the US and Singapore. The onus is on the HS industry to act responsibly and avoid making inappropriate claims. There are unethical companies, however, that will seek to boost sales by making inappropriate claims. These companies may abuse the lack of oversight by making claims that appear legal and deceive consumers into believing the HS products can treat or prevent disease.^{26, 29} Premarket interventions can prevent inappropriate claims as the RAs would be able to reject such claims before granting market authorization.

An ideal premarket regulatory regime should require all companies to prove HS efficacy via randomized clinical trials (RCTs), similar to the premarket regulatory framework for pharmaceutical products. This would allow only products with proven efficacy to reach the market. However, RCTs can be costly, and HS companies may not have the economic resources as there are no avenues to patent their products. Additionally, it may not be practical to expect RCTs to be conducted for all types of claims. Instead, it would be more prudent for the various HS claims to be substantiated by appropriate levels of evidence, based on the nature of the HS and their risk profiles.

Establishing GMP

GMP-compliant companies are better able to assure HS quality and safety as they have consistent manufacturing processes and cross-contamination

chdc

VALSTEAM Adca
valsteam.com

PRODUCTS MANUFACTURED IN PORTUGAL

High purity systems require high quality products.
That's what Adca Pure is all about.

**PURE CONTROL
CLEAN EFFICIENCY
TOTAL RELIABILITY**

AdcaPure
Pharma, Food, Chemical & Cosmetic

STEAM TRAPS | SAMPLE COOLERS | HUMIDITY SEPARATORS
CONTROL VALVES | PRESSURE REDUCING VALVES | PRESSURE SUSTAINING VALVES

Zona Industrial da Guia | Pav. 14 - Brejo | 3150 - 467 Guia PBL | Portugal
+351 236 959 060 | adca@valsteam.pt | www.valsteam.com



ASEAN Traditional Medicines and Health Supplements Product Working Group

prevention programs in place. Currently, there is a lack of national and international GMP standards specifically for manufacture of HS. It is essential to establish internationally acceptable GMP standards to avoid quality issues. The manufacture of HS requires appropriate process controls, suitable equipment, specialized skills, and knowledge.

The occurrence of several quality-related incidents convinced US FDA to establish GMP specifically for the manufacture of HS. The US FDA also noted that because HS, unlike food products, were packaged into dosage forms such as tablets and capsules, it would be inappropriate for HS manufacturers to adopt GMP established for food manufacturers. Although GMP compliance will increase manufacturing costs, it will help improve consumers' confidence in HS. In the long run, this will benefit the HS industry, the RA, and the consumers. Upon implementation of the GMP inspection standard, there should be periodic audits by RAs to ensure continued GMP compliance by the manufacturers. Periodic audits are necessary as HS companies were still found to be noncompliant to GMP during ad hoc audits conducted by the US FDA despite the establishment of GMP standard for HS manufacturers.³⁰ The 2003 Pan Pharmaceutical debacle in Australia is a classic example of the importance of regular GMP audits.

RAs can also explore other options beside implementing regulatory controls to address quality problems. These include encouraging HS companies to undergo voluntary third-party (independent) GMP certification, coordinated by industry associations. Currently, reputable third-party organizations such as the US Pharmacopeia (USP) and NSF International conduct quality testing of products as well as GMP inspection of manufacturing facilities.³¹⁻³²

HS products that bear these organizations' stamps indicate that the manufacturers are GMP compliant. These voluntary independent certifications may provide a form of quality assurance to HS consumers. RAs can encourage companies to undergo such certification by educating the public and

health care professionals about the important role such organizations play. They could also provide guidance to assist HS companies in selecting the correct organizations³³ and to single out products that are legally misbranded, or do not comply with the certifying organization's specifications.³⁴

These certifications could also help ease the strain on the limited resources by complementing the RA efforts in market surveillance and GMP audits, especially for overseas HS manufacturers. Organizations such as USP have established offices in countries such as India and China to facilitate the certification of HS manufacturers in these countries. RAs can also help encourage some form of industry self-regulation through formation of associations such as the Health Supplements Industry Association of Singapore, Food Supplements Europe, and the Council for Responsible Nutrition in the United States. The associations could establish their own code of ethics and mutual agreements on GMP and quality standards, thus increasing the likelihood that companies will be GMP compliant. In some cases, the associations have established their own GMP standard specifically for the manufacture of HS despite the lack of a regulatory GMP standard. Overall, industry initiatives may complement the efforts of RAs to safeguard public health and help to ease the strain on the limited resources of RAs.

Harmonization of regulatory requirements

Most regulatory standards for HS are currently not harmonized. In some countries such as China and Australia, HS are required to be registered with the RAs while in many other countries, premarket licensing or approvals are not mandatory. This leads to a diverse range of regulatory requirements for the HS industry to manage.

Harmonization of HS regulatory requirements could enhance consistency, efficiency, and cost-effectiveness for both RAs and the industry. It would facilitate cooperation and collaboration among different RAs in a highly globalized world with interconnected trade. Sharing information among different RAs can facilitate the detection of adulterated or poor quality

HS and help avoid public health crises. Harmonization is also beneficial for companies as it can reduce number and amount of regulatory submissions required and hence, reduce registration time and regulatory cost.³⁵ It has been shown that harmonized requirements and the resulting reduced cost of product registration have encouraged pharmaceutical companies to invest more in research. The same outcome may apply to the HS industry if the regulatory requirements for HS are harmonized.

However, harmonization may create economic issues for countries that have insufficient resources or expertise. Moreover, the large variation of HS products and formulations in different countries may compound the difficulty of achieving harmonization. Nevertheless, harmonization should be pursued.³⁵ International organizations such as the WHO and the Food and Agriculture Organization of the United Nations as well as countries with relevant expertise can help countries that are lacking, through training of the regulators. ASEAN member states have been harmonizing their regulatory requirements for HS and collaborating actively with one another. Despite differences in cultural, political and socioeconomic background among ASEAN member states, significant progress has been achieved, indicating that harmonization of HS regulatory requirements at the regional or international level is possible.

Conclusion

The demand for HS is expected to grow considerably, attracting many companies to have a slice of the growing market. It is still largely a caveat emptor (buyer beware) market where tighter worldwide regulatory control for HS appears necessary. RAs should implement appropriate HS regulatory schemes to safeguard public health, but without severely affecting the consumers' access to affordable products. As all RAs have limited resources in terms of manpower and funds, an appropriate risk-based regulatory scheme is critical. ■

References

1. Singapore Health Sciences Authority. "ASEAN Guidelines on Labeling Requirements for Traditional Medicines and Health Supplements." www.hsa.gov.sg/content/dam/HSA/HPRG/Complementary_Health_Products/Annexes/ANNEX%20IX%20ASEAN%20GL%20on%20Labeling%20Requirements%20for%20TMHS.pdf.
2. European Commission. Food Safety, Labeling and Nutrition: "Food Supplements." http://ec.europa.eu/food/safety/labelling_nutrition/supplements/index_en.htm.
3. US Food and Drug Administration. "Dietary Supplements." <http://www.fda.gov/Food/DietarySupplements>.
4. Feldman, Monica. "The Impact of Regulation on the Market Value of Nutraceuticals." Presented at Discover Global Markets: Healthcare and Life Sciences Business Forum Series, 17-18 November 2015, Minneapolis, Minnesota. http://export.gov/minnesota/build/groups/public/@eg_us_mn/documents/webcontent/eg_us_mn_080867.pdf.
5. O'Connor, Anahad. "New York Attorney General Targets Supplements at Major Retailers." *New York Times*, 3 February 2015. http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/?_r=2.
6. Lockwood, G.B. "The Quality of Commercially Available Nutraceutical Supplements and Food Sources." *Journal of Pharmacy and Pharmacology* 63, no. 1 (2011): 3-10.
7. Harel Z, et al. "The Frequency and Characteristics of Dietary Supplement Recalls in the United States." *JAMA Internal Medicine* 173, no. 10 (May 2013): 926-928.
8. Singapore Health Sciences Authority. "HSA Alerts Public to 'OxyELITE Pro'—an Unregistered Medicinal Product Linked to Serious Liver Injuries." www.hsa.gov.sg/content/hsa/en/News_Events/Press_Releases/2013/OxyELITE_Pro.html.
9. Venhuis B.J., et al. "Capsule Shells Adulterated with Tadalafil." *Forensic Science International* 214 nos.1-3 (2012): 20-e22.
10. US Food and Drug Administration. "FDA Issues Warning Letters to Dietary Supplement Firms in Colorado and Texas for Promoting Unapproved Products as Drugs." FDA News Release, 6 September 2012. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm318445.htm.



zenon

YOUR INDUSTRIAL SOFTWARE FOR GMP AUTOMATION RIGHT OUT OF THE BOX



- ▶ *ISA 88 – Batch Control and Electronic Batch Records*
- ▶ *Historian & Reporting solutions*
- ▶ *Line Management*
- ▶ *FDA Part 11 Compliance*
- ▶ *GAMP 5 – software category 4*

www.copadata.com/pharmaceutical



COPADATA
do it your way

Microsoft Partner

Gold Application Development
Gold Intelligent Systems
Silver Cloud Platform

