An essential guide to understanding the implications of product quality.

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Publicized contaminations have focused the world's attention on safety

Several highly publicized contamination incidents have underlined the need for assuring the safety and traceability of food products and dietary supplements. In 2013, horse meat was detected in European beef products. A year earlier, chromium was detected in Chinese gelatin capsules. And recently the U.S. Food and Drug Administration presented sweeping rules aimed at preventing the contamination of produce and processed foods, which has sickened tens of thousands of Americans annually in recent years. These incidents have had significant repercussions in the marketplace, increasing pressure on suppliers of food, health and nutrition goods to deliver high-quality products. A recent Mintel survey of British consumers found that traceability of food has become increasingly important to them. And a recent survey in France by Agence Bio revealed that more than 50 percent of consumers are looking for information about the origin of ingredients when purchasing food products.

A commitment to safety and quality

Capsugel has been producing innovative dosage forms for nutrition and pharmaceutical markets for more than 100 years. Our company is one of the world's leading purchasers of corresponding key raw materials for capsules—including gelatin and alternate polymers such as hypromellose (HPMC) and pullulan. The quality of our finished dosage forms strongly depends on the quality of their ingredients, which is why we have created an extensive compliance program focused on meeting the strictest international regulatory requirements and also established a robust quality system for sourcing key raw materials—all aimed at safeguarding the integrity of the supply chain from raw materials into finished product and assuring safe use in food supplements. Upon product completion, we then acquire the proper certifications—if needed—to go to particular markets. This white paper reviews best practices for mitigating risks and ensuring the quality, safety and traceability of empty capsule products and demonstrates how our programs and processes actually benefit the companies and customers who work with us.

STAYING AHEAD OF QUALITY INITIATIVES: *THE GOOD NEWS*

When high levels of chromium were detected in gelatin capsules made in China, Capsugel was unaffected by the issue, primarily because of the quality control and quality assurance programs already in place. Capsugel's existing gelatin purchase specifications already included chromium restrictions when the incident occurred. So in April 2013, when the United States Pharmacopeia-National Formulary monograph for raw pharmaceutical grade gelatin was revised to include testing for heavy metals, Capsugel had good news for its customers: they were informed that Capsugel was already in compliance with the new monograph before it was even issued.

The two most important principles of quality control

Mitigating risks through a comprehensive quality control and assurance program—from the purchase of key raw materials to manufacturing, packaging and delivering finished products—helps to ensure the safety and quality of goods sold in the health and nutrition and pharmaceutical marketplace. Purchasers of empty capsules and food supplement product ingredients should ensure that they source their products from companies that meet two basic criteria: (1) a regulatory compliance monitoring program that anticipates and proactively responds to the continuously evolving global food-safety standards; and (2) a robust quality system compliant with all applicable standards.

MONITORING GLOBAL FOOD STANDARDS

Capsugel has the in-house expertise for making sure we meet regulatory standards for healthcare products anywhere in the world. In addition to our regulatory expertise, our quality assurance managers have extensive experience in the health and nutrition market, due to our customer and end-user contacts. We are also an active member of many trade associations operating at different levels, including the International Alliance of Dietary/Food Supplement Associations (IADSA), Food Supplement Europe (FSE) and several regionally based associations. Monitoring these associations is imperative to staying abreast of the evolving marketplace, gaining insight into current guidelines and learning about upcoming regulatory requirements.

CREATING A STANDARDIZED QUALITY COMPLIANCE SYSTEM

At Capsugel, we know how to meet the challenge of complex global regulations. Our international operations go beyond the minimum Good Manufacturing Practices (GMP) and quality system requirements, factoring in local regulatory or GMP requirements at the site level. To attain standardized quality compliance, we have created an organizational structure that selects the pertinent standards for each market segment. We have also developed corporate auditing tools to ensure proper execution and ongoing monitoring, not only by our own internal auditing but also by hosting audits from certification bodies and customers.

With our rigorous regulatory monitoring and quality systems, our customers can be assured that raw materials, colorants and other ingredients used in hard empty capsules meet all standards with minimal risk of recalls or other sanctions. Further, all products are manufactured according to a high level of GMP, suitable for and exceeding the regulatory requirements for the manufacture of food ingredients.

REPUTATION IS BUILT ON CONSISTENT PERFORMANCE

1	The number of years required to qualify a new gelatin source, covering four distinct evaluation stages
3	The number of filtration steps applied to liquid gelatin in our manufacturing plants
7	The number of visual assessments of capsule samples per day per line, done in addition to colormetric measurement of each gelatin transfer tank
15	The number of regulatory references (e.g. USP, JP, FCC, OIE, FDA, etc.) that forms the basis of our gelatin purchasing specifications
20	The number of categories of quality and regulatory documents that our CSR team can assess quickly to avoid shipment delays
152	The number of parameters we assess during bi-annual audits of our qualified gelatin vendors
CONSTANTLY	The frequency rate at which we monitor real-time temperature and humidity in our warehouses and distribution centers

Quality compliance in practice: Integrity at every stage of the product life cycle

With resources ranging from a global auditing team to a worldwide network of scientific and technical experts, Capsugel supports a best practices approach throughout each of the key stages in the life cycle of a capsule—raw material sourcing, manufacturing, release and distribution and product certification.

Raw Material Sourcing

The art of manufacturing empty capsules has been honed to a fine science through the application of technology and more than 100 years of experience and innovation. However, the evolving challenge is guaranteeing the safety of the finished products and the traceability of key raw materials. All capsule manufacturers must validate the quality of all key raw materials used along with the entire supply chain. To do this successfully requires robust sourcing and qualification processes.

Capsugel has established a four-step program to protect its supply chain:

Raw Material Sourcing

STEP 1 RAW MATERIAL PURCHASE SPECIFICATION SYSTEM

Before we buy raw material from suppliers, it must meet our purchase specifications outlined in our Raw Material Purchase Specification System—contractually enforceable standards that Capsugel has instituted based on worldwide regulations and guidelines. Capsugel's purchase specifications apply to all of its facilities worldwide and are tightly focused on controlling contaminants and impurities.

Raw Material Sourcing

STEP 2 SUPPLIER SELECTION AND QUALIFICATION PROGRAM

Capsugel's Supplier Selection and Qualification Program guarantees that our hard capsules meet the highest standards for quality, traceability and integrity. This core five-phase program requires critical raw materials suppliers to undergo an intensive selection and qualification process to make sure they meet the most stringent regulatory and industry standards that exist anywhere in the world.

Raw material purchase specification standards

- Purity criteria of the most strict regulatory references applicable on the ingredient: (EU) Regulation 231/2012 lays down specifications for food additives, including specific purity requirements concerning colors for use in foodstuffs, Codex Alimentarius JECFA, US CFR, FCC, JSFA, Pharmaceutical standards in Europe, U.S. and Japan (EP, JP, USP)
- Impurity limits as per regulatory references or guidelines such as:
  - » EU Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs
  - » ICH Q3D elemental impurities guideline
  - » USP proposed General Chapters <232> and <233>, Residual Solvents ICH Q3C
- Viral safety guarantees for animal-derived ingredients based on recommendations of the OIE Terrestrial Animal Health Code
- Biological safeguards as it relates to GMO, as defined by Regulation (EC) n° 1829/2003 on genetically modified food and feed and by the Regulation (EC) n° 1830/2003 concerning the traceability and labeling of GMO
- Controlled use or absence of allergens as defined by Regulation (EU) No 1169/2011 on the provision of food information to consumers

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Raw Material Sourcing

STEP 3 SUPPLIER PERFORMANCE MANAGEMENT PROGRAM

Once a supplier has successfully passed the qualification process, it enters Capsugel's Supplier Performance Management Program, an ongoing evaluation process designed to assure supply chain traceability and finished capsules that comply with the highest integrity standards.

Supplier Performance Management Program

- Constant testing to the highest standards
- Regular in-depth onsite audits of suppliers
- Continuous monitoring

Raw Material Sourcing

STEP 4 GLOBAL PURCHASE STRATEGY

Capsugel's Global Purchase Strategy is designed to make sure we have a reliable supply chain that provides uninterrupted access to critical raw materials. This purchase strategy involves establishing long-term partnerships with numerous globally qualified suppliers that have multiple production sites and sources. The raw-material market is continuously screened to make sure that we have a sufficient number of suppliers to call upon at any given time, and we share information with them on the latest regulations and provide them with ongoing training.

EU & FVO RECOGNIZED

Recent findings from the European Union (EU) Food and Veterinary Office's (FVO) inspection of gelatin manufacturers in India show that our quality control and quality assurance programs are achieving their goals. The inspection was carried out as part of the FVO's effort to evaluate compliance with EU standards, both within the EU and in countries that export to the EU. When the FVO inspected two of Capsugel's Indian gelatin suppliers in 2012, both successfully passed. Moreover, the FVO recognized Capsugel as an important industry representative with relevant knowledge when considering future regulatory changes pertaining to gelatin.

5-PHASE SUPPLIER SELECTION AND QUALIFICATION PROGRAM

1. **Preliminary investigation:** Reviews the supplier's quality system, state of manufacturing technology and scope of products and services offered and determines the supplier's performance metrics in detail.
2. **Manufacturing suitability evaluation:** Assesses the crucial issue of whether the supplier's raw material is compatible with Capsugel's manufacturing processes and protocols.
3. **Production trial:** Implements supplier's raw material in large-scale, high-volume production trials at various Capsugel sites to confirm both finished capsule quality and manufacturing efficiency performance levels.
4. **Onsite audit:** Performs a traceability exercise and quality system check covering over 150 parameters to ensure compliance with applicable Capsugel standards.
5. **Acceptance contract:** Formalizes the technical and commercial requirements and expectations, including both initial scale-up support and on-going quality.

The standard for quality manufacturing, release and distribution

WORLD-CLASS MANUFACTURING SITES

Capsugel manufacturing sites have successfully passed various inspections and adhere to all standards for safe products, including those for extended traceability—from incoming receipt to final shipment. We use hygienic equipment designed for product contact surfaces and employ food-grade and tamper-proof packaging. Given the cleanliness of the sites and their stringent control over capsule manufacturing operations, our capsules are manufactured to maintain a high microbiological quality level without the need for preservatives or sterilization using irradiation or ethylene oxide.

STRINGENT CAPSULE RELEASE TESTING

Our release requirements comply with purity and microbiological specifications that apply to the capsules' end use as food supplements and pharmaceutical excipients. Our validated test methods contribute to a comprehensive release process, allowing customers to be confident in the quality of the capsules they receive.

Reduced testing—the benefits of a certified vendor program

Capsugel provides a partnership initiative with customers facilitated through a certified vendor program that will allow reduced testing through acceptance of test procedures and the use of Certificate of Analysis results. The reduced testing programs typically involve analytical testing (Loss on Drying, Disintegration, Weight) and micro testing. The program components include a history of quality based on consistency of testing results and procedures and batch-to-batch consistency and reproducibility. Because of Capsugel's robust quality systems, including audits and certification of all major ingredients and suppliers, in combination with tight process control and high process capability, supported by customers' audits of Capsugel manufacturing and laboratory facilities—Capsugel has been able to maintain Reduced Testing Protocols with a number of major pharmaceutical and health and nutrition customers. The benefits accrued through a Reduced Testing Protocol include the elimination of redundancies and both fixed and variable cost savings through reduction of sampling, micro and analytical testing. Reduced testing also provides greater flexibility for micro and analytical testing—a greater reduction in the overall cycle time.

INTEGRITY IN TRANSPORTATION AND SUPPLY CHAIN

To ensure reliability throughout the supply chain, a robust quality system must qualify carefully selected certified partners. It must also require these partners to keep in-depth knowledge of product sold and conduct regular training. Likewise, safeguarding a product's properties during transport is crucially important. To do so, Capsugel carefully selects and qualifies its transporters and—through documented quality requirements—makes them aware of the nature of the product being shipped and the required conditions.

Product certification creates market opportunities

Product certification is imperative when targeting certain markets, some of which are growing at exponential rates. (For example, 35 percent of supplement users in the United States say that a vegetarian source is important when choosing a supplement—up from 26 percent in 2006*.) Selecting the right capsule ingredients becomes important when products labeled Kosher or Halal are exported to certain markets and require religious certifications. It may also be necessary to use non-animal ingredients in capsules sold to vegetarian consumers. HPMC-based capsules are suitable for use with organic dietary supplements in Europe while in the United States, pullulan capsules are those approved for use with organic ingredients in order to accommodate "made with organic ingredients" label language.

*Natural Marketing Institute, Supplement/OTC/Rx Database (SORD) Overview, November 2011.

Capsugel product certifications

NON-GMO CERTIFICATION

Capsugel empty capsules are "non-GMO" and are not produced from nor contain genetically modified organisms (GMOs). The test method and acceptance standards we use support our non-GMO claims and are based on a method that relies on PCR technology (Polymerase Chain Reaction), which allows magnification to ensure no match with genetically modified DNA segments. Additionally, Capsugel products such as Vcaps® capsules, Vcaps® Plus capsules and Plantcaps® capsules are Non-GMO Project Verified. The proprietary technology and design of Capsugel's Vcap Plus capsule offers a unique solution for either liquid or powder delivery. The Non-GMO Project is North America's only third-party verification and labeling for non-GMO foods and products. Verification requires ongoing testing and ensures rigorous traceability and segregation practices are followed in order to meet finished product integrity.

VEGETARIAN AND VEGAN CERTIFICATION

Capsugel products such as DRcaps® capsules, Vcaps® capsules, Vcaps® Plus capsules and Plantcaps® capsules are certified by the Vegetarian Society of UK and the Vegan Action organization of the United States. That means they are certified free from animal-derived ingredients and are cruelty-free with no animal testing.

KOSHER CERTIFICATION

Capsugel offers three Kosher capsule certifications for empty gelatin and vegetarian capsules. Consult with Capsugel's Customer Service Organization for specifics related to the Kosher certifications.

HALAL CERTIFICATION

Capsugel offers four Halal certifications for capsule products made from H bovine gelatin and vegetarian polymers. Consult with Capsugel's Customer Service Organization for specifics related to the Halal certifications.

Product integrity for peace of mind

The safety of foods, dietary supplements and pharmaceutical products is a major concern for consumers, governments and the nutrition industry. With its insistence on quality, safety and traceability, Capsugel is setting the standard for product integrity. The value for our customers is clear: they can rest assured that the capsules they buy will always comply with increasingly strict regulations wherever their products are sold.

At Capsugel, we strongly believe that staying ahead of the product integrity curve makes good business sense—and that establishing a reputation for marketing safe products is crucial for the industry in general. We take pride in optimizing our customers' ideas and accelerating their time to market, while also maintaining a steadfast focus on product integrity.

Our efforts to assure the integrity of our products, outlined in this white paper, ensure our customers' peace of mind.

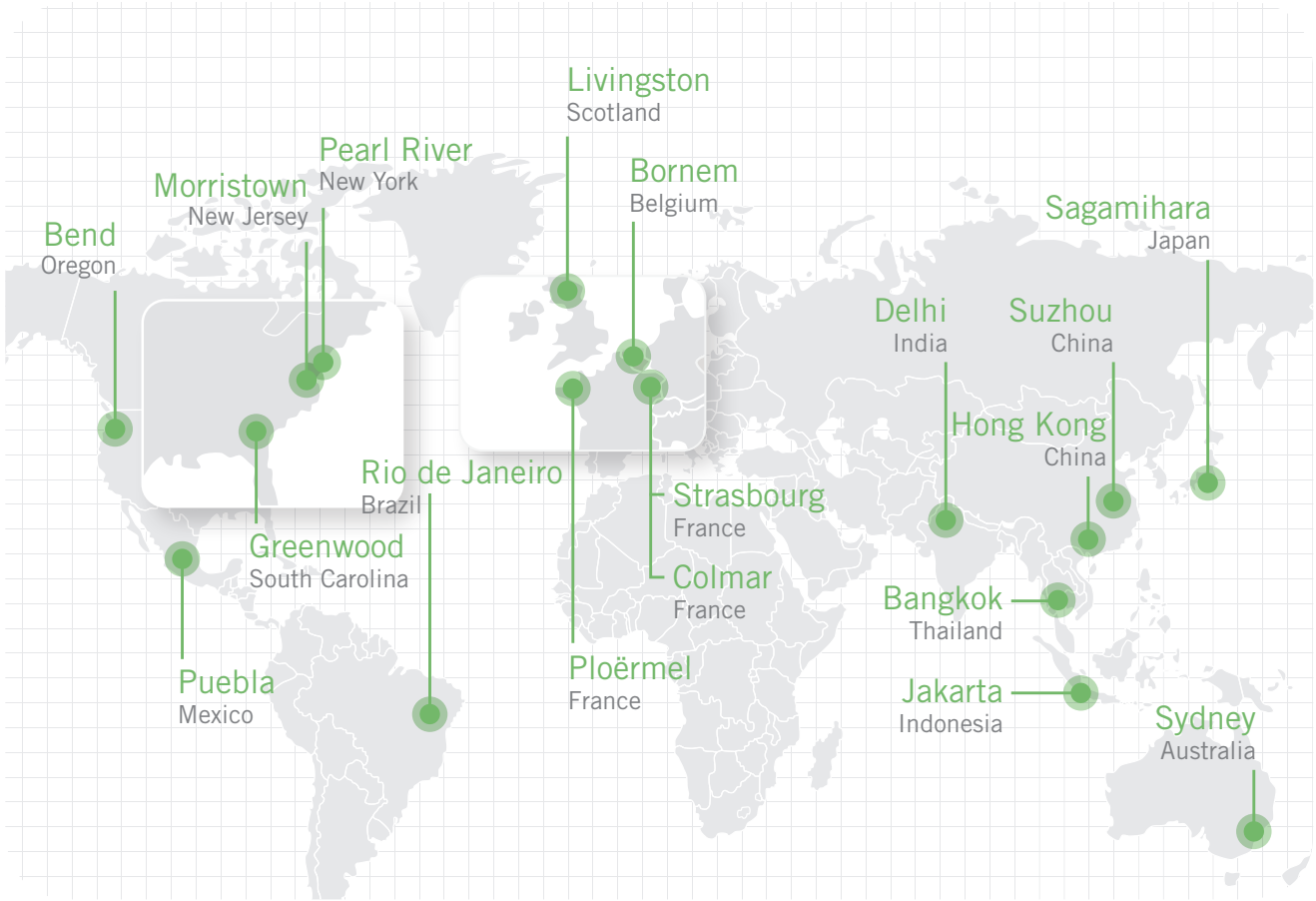
Capsugel's global footprint ensures formulation expertise and certainty of supply.

Our customers span the world, and so does Capsugel. Each year we produce close to 200 billion capsules for more than 4,000 customers in more than 100 countries. Our vast production capacity helps us effectively respond to changing marketplace demands no matter where our customers are located—providing you with the peace of mind that your dosage-form requirements will be met rapidly and with world-class quality.

We manage dozens of customer formulation projects every year across an array of challenges, from solubility enhancement to taste-masking.

Capsugel operates 24/7 in manufacturing locations, state-of-the-art Product Development Centers and multiple business offices around the world.

To work together or learn more, contact us at capsugel.com.



Our global presence, industry-leading capsule products and innovative drug delivery technologies translate into shorter go-to-market time for Capsugel customers.