

# Importing dietary supplements from American firms under a GMP framework

OUTSOURCING

**M**any European and Asian nutrition firms have reaped the benefits of outsourcing their contract manufacturing needs to American firms decades ago. However, with the ever-weakening US dollar, many nutrition companies are just recently discovering the benefits of working with US companies. The most significant issue involved with foreign companies working with American nutrition companies is the ability to register their products with the local governments. This not only requires compliance with good manufacturing practices (GMPs) in the US, but also compliance with GMP guidelines in foreign governments and third party guidelines. With industry acronyms such as GMP, DSHEA and NLEA, it's facile for one to get lost in the jargon. Compound the sheer volume of contract manufacturers, and the choice becomes near impossible. Therefore, the following is a list of things to look for when reviewing a contract manufacturer.

## REGULATORY AFFAIRS

For firms located in Europe or Asia, the issue of regulatory compliance is of primary importance. This not only requires a contract manufacturer to comply with good manufacturing practices (GMPs), but more importantly a willingness to work with the marketer on registering the product with the local ministry of health and/or regulatory body. With several government bodies and non-government organizations attempting to harmonize GMPs for the industry, discord and disagreement remains between the public and private sector. Much to the chagrin of multi-national drug firms and foreign governments, dietary supplements in the US are regulated as foods **not** as medicines or drugs.

To remedy this potential problem, the

US FDA issued a final rule called "Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body." This statement along with highly anticipated dietary supplement GMPs is how the FDA is hoping to govern the industry as it does pharmaceuticals. Separately, the Codex Alimentarius Commission (Codex), an arm of the World Health Organization (WHO) and World Trade Organization (WTO) is attempting to harmonize GMP guidelines modeled after the EU's adoption of regulating dietary supplements as drugs. Finally, non-government organizations such as the National Nutritional Foods Association (NNFA), NSF International (NSF) and the United States Pharmacopeia (USP) have introduced third party certification programs for GMP compliance.

For the past several years, GMPs have become a staple in industry discussions, forums and articles. GMPs are guidelines that provide a framework of minimum requirements to produce a dietary supplement which is pure, efficacious and safe. When evaluating a contract manufacturer, it is highly recommended that you make sure that they comply with current and upcoming GMP requirements. This should include third party certifications as well as compliance with FDA pharmaceutical cGMPs. The backbone of any GMP program requires documentation, process validation, and most importantly, the sage mantra of "say what you do, and do what you say." Due to the lax government stance, the



Figure 1

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spectrum of contract firms varies from GMP compliant facilities to garage type operations. M. Amirul Karim, president of US-based NHK Laboratories, Inc., said "Our commitment to global regulatory compliance and quality is evidenced by our multi-million dollar investments in plant, equipment, personnel and most importantly a proactive voluntary election to be regulated as a drug firm in the US. In addition, we've received prestigious third party certifications from the NNFA GMP and NSF GMP programs."

## ANALYTICAL LABORATORY

**G**MPs are far more than cleaning plant and equipment. It's the validation of formulas and procedures. The objective is to ensure that the end user is using a product which is the drug it purports itself to be, is efficacious and extremely safe to use.

True GMP compliance is achieved by ensuring that the suppliers of raw materials are also following GMP guidelines. This encompasses physical plant audits of supplier facilities, personnel and procedures. The GMP process begins before the production of a batch even takes place.



Figure 3

"All raw materials are quarantined immediately upon receipt, and are then tested in our on-site analytical laboratory. Test parameters include identity and several additional qualitative and quantitative analyses" said Mr. Karim. If the raw materials meet the predetermined qualified specifications, they are released from the quarantine area, and are sent to compounding, unit dosing and finally packaging.

True compliance with GMPs can only be achieved by validating processes and formulas. Validation is substantiated by having an analytical laboratory confirm the identity, purity, potency and stability of a product. Accordingly, test parameters can be verified cost effectively in a commercial manufacturing operation if the laboratory analyses are conducted on-site. Universal GMPs require all raw material lots to be tested for identity, purity and potency prior to compounding. According to GMP principles, all in-process mixes must be tested for uniformity. Lastly, the finished product must be tested for potency and stability.

Released materials are compounded in one of several large V-Blenders to achieve optimal blend uniformity (Figure 1). Blended powders are unit-dosed into capsules or tablets using high-speed CGMP equipment including Bosch GKF 2000

capsule fillers (Figure 2). After the batch has been unit dosed, the bulk product is packed for consumer sale (Figure 3).

"During the manufacturing process, our quality control and quality assurance staff ensures that the blends are uniform, and that the finished product meets our predetermined qualified specifications, and finally post-production efficacy testing using HPLC, GC, UV-VIS and AA methodology to ensure the product is efficacious and stable" said Mr. Karim.



Figure 2

## GMP PRODUCTION PROCESS

**A**t NHK Laboratories, Inc., all raw materials are quarantined immediately upon receipt.

The raw materials are then extensively tested in our state-of-the-art analytical laboratory using HPLC, GC, FT-IR, AA and other methodologies to ensure the purity, potency and safety of the ingredients. Once the NHK Laboratories quality assurance team has qualitative and quantitative proof that the ingredient is pure and safe, the raw

material is released into the general warehouse.

After release, raw materials are picked, weighed and "kitted" on calibrated scales in a new multi-million dollar class 100,000 clean-room processing facility. The "kits" are particle sized or blended in one of several large fluid-bed granulators or V-blenders. After the batch has been released from the compounding department, the blended powder is gravity-fed to one of several high-speed compression lines. Then new high-speed tablet presses and capsule fillers are capable of manufacturing more than 2,000 pills per minute. With a daily production capacity of approximately 15 million tablets and 12 million capsules, the company is capable of handling any batch size.

The unit-dosed batch is sent to coating shortly after compression, where an aqueous, solvent or sugar coating is applied to the tablet, creating a pharmaceutically elegant dosage form. After manufacturing for capsules and coating for tablets, each batch is then inspected for any defects, and capsules go one step further into polishing, to ensure that what's inside the capsule isn't also on the outside.

After the batch has been inspected and polished, NHK's quality assurance team

conducts additional analytical tests to ensure the product meets predetermined "qualified" specifications. Additionally, a batch record review is completed to account for any variations or deviations prior to distribution or finished product packaging.

## MAKING THE CHOICE

**S**o how do you choose the right contract manufacturer? When importing American manufactured dietary supplements, documentation evidencing compliance with GMPs becomes mandatory to a long and fruitful relationship between contract manufacturer and marketer. Most foreign governments require notarized or legalized copies of GMP certificates, relationship letters, free sale certificates and batch formularies including stability studies and analytical methodologies. Due to the lenient US regulatory stance, many US firms are unable or unwilling to comply.

In addition to regulatory positions, the obvious business objectives must be met. Timely delivery of merchandise, and competitive prices are issues to consider when reviewing any supplier. Most of the objectives can only be met by partnering with well-funded companies capable of achieving economies of scale. This includes partnerships with global raw material manufacturers of raw vitamins, minerals and nutraceutical ingredients. According to Mr. Karim it's important to be dealing with a contract manufacturer that has the scale and global contacts to buy from ingredients manufacturers, not brokers. "We purchase our ingredients directly from the manufacturers. This includes maintaining a strong relationship with vitamin, mineral and fine chemical firms all over the world. This becomes especially important when purchasing ingredients with price volatility such as Ubidecarenone (Co-Enzyme Q10) and Thioctic Acid (Alpha Lipoic Acid)."

When reviewing potential American contract manufacturers, the decision should be made on physical plant audits of the contract manufacturing and establishing relationships with the personnel. Establishing a rapport with the contract manufacturer, and keeping open lines of communication are the cornerstones of success to any relationship.

