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Current Good Manufacturing Practice for Dietary Supplements—Role of the Analytical Laboratory

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June 25, 2008 marked the first date by which dietary supplement manufacturers and distributors must comply with the Final Rule on Current Good Manufacturing Practice (cGMP) for Dietary Supplements. Companies with 500 or more full time equivalent employees (FTEEs) are now subject to FDA inspection for compliance with the rule. Companies with 20 to 499 FTEEs face June 25, 2009 as the D-Date. Those with less than 20 have until June 25, 2010.

Quality assurance is fundamental to cGMP compliance. The rule defines "quality" to mean that a dietary supplement meets established specifications for identity, purity, strength and composition. Specifications must also be set and met for limits on contaminants, such as heavy metals, solvent residues and harmful microorganisms, in finished products.

Specifications are incorporated into the Master Manufacturing Record (MMR), which is the complete set of instructions for making and testing the product. Batch-to-batch uniformity—assurance that each and every batch conforms to specifications—occurs as long as each step in the MMR is performed and checked. For each lot manufactured, a Batch Production Record must be prepared. The Batch Record provides documentation that every step in the MMR was in fact performed, that the finished dietary supplement meets specifications,

and that quality control personnel verified this, before the product is released for distribution.

Under the new rule, laboratory analysis of both raw materials and finished products is in integral part of the production process. The rule devotes an entire subpart to requirements for operation of an analytical laboratory. As stated in the rule, "laboratory facilities must be adequate to perform whatever tests and examinations are necessary" to determine if specifications are met for raw materials, materials in process and finished products. The laboratory may be in-house or an outside contract analytical lab (CAL).

Laboratory operations must follow written procedures and use scientifically valid analytical methods. Random sampling plans must be used to obtain representative samples for testing components, in-process materials and finished products. And most importantly, the laboratory must keep complete, readily accessible records.

The laboratory performing the quality control testing, whether an in-house lab or a third party contract lab, must use methods that are appropriate for the tests performed and the materials being tested. Suitable methods include those from compendia such as the USP monographs, methods validated by organizations such as the AOAC, methods published in peer-reviewed journals and in-house methods. In order to be scientifically

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valid, in-house methods are put through a formal validation process that demonstrates the ability of a method to produce reliable, repeatable results.

Key to cGMP compliance is verification that each component in a dietary supplement is what the label says it is; meaning that it meets established specifications for its identity. There are two categories of components: dietary ingredients and non-dietary ingredients such as excipients. The Dietary Supplement Health and Education Act of 1994 (DSHEA) defines five categories of substances that qualify as dietary ingredients: vitamins, minerals, herbs, amino acids and dietary substances used to increase the total daily intake along with concentrates, metabolites, constituents, extracts or combinations of these ingredients. All dietary ingredients are components, but not all components are dietary ingredients, and the testing requirements are different for the dietary and non-dietary ingredients.

In the past, manufacturers often relied on the raw material supplier's certificate of analysis (C of A) for a particular lot of a dietary ingredient as proof of its authenticity. This is no longer acceptable: the cGMP rule requires confirmation of the identity through examination or testing, for every lot. Organoleptic examination (look, smell, taste) may be performed for ingredients such as botanicals that have unique organoleptic characteristics known to experts, as long as the quality control personnel performing the examination are qualified to do so. Ingredients that cannot be identified organoleptically must be lab tested, using a scientifically valid analytical method.

The FDA has issued an interim final rule for a process through which a manufacturer may petition

the agency for an exemption from the one hundred percent identity testing requirement for a dietary ingredient. The manufacturer must submit data in support of its case that reduced testing is adequate to ensure that the ingredient is what it's represented to be. Assembling data of sufficient quality and quantity to persuade FDA will require, in most cases, a substantial amount of initial testing. The manufacturer will need to adhere to one hundred percent testing while the FDA reviews the petition, however long that takes.

When it comes to authenticating non-dietary ingredient components, the rule permits greater latitude. Each lot may be tested if the manufacturer chooses to do so. As an alternative, the supplier-issued C of A may be used as proof of identity, as long as reliability of the C of A has been established, through verification of the test results listed on the C of A. This means the manufacturer will, for many components, need to conduct independent tests. The rule adds an additional requirement to "periodically confirm the supplier's certificate of analysis", although how often this should be done is not specified. Quality control personnel must review and maintain documentation used to qualify the supplier.

All of this adds up to a dramatic increase in the amount of testing, which in most cases requires an analytical laboratory, that will be conducted on dietary supplements in the coming months and years—before they are blended, packaged and labeled.

Finished dietary supplements must also be tested, however, the rule does not require testing every batch. Again, the manufacturer may test every batch if it chooses to do so. Alternatively, the rule

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permits testing “subsets of finished dietary supplement batches.” It is up to the manufacturer to determine testing frequency; the FDA does numerically dictate what constitutes a subset of finished batches. A statistically valid sampling plan should be used to define the subset. The manufacturer must test against one or more of the product's specifications for identity, purity, strength and composition. Conformance to that specification must form a sound basis for determining that the manufacturing process effectively produces a product meeting all specifications. The manufacturer must document how it determined that verification of the tested specification confirms this.

Meeting the testing requirements for raw materials and finished products requires careful selection of analytical methods and equipment. Product-specific testing plans should be designed and implemented by qualified technicians. Manufacturers relying on in-house laboratories must equip their labs with an array of analytical equipment and staff them with analytical chemists who are both skilled in using the equipment and experienced in performing complex analyses on a wide range of ingredients. If this is not practical, contract analytical laboratories with expertise in analysis of particular types of ingredients are available to do the work.

Analytical techniques that are applicable for testing dietary ingredients and finished products include the following:

HPLC (High Performance Liquid Chromatography)

Chromatography is used to separate and analyze the chemical constituents of a substance. Chromatography was invented in 1906 by a Russian bota-

nist who used it to separate plant pigments from an extract of green leaves. The extract was poured into a column containing calcium carbonate. As the liquid flowed down the column, the various pigments adsorbed at different locations, producing visible horizontal bands. Each band represented a different color, producing what came to be known as a chromatogram.

HPLC is a very sensitive form of chromatography that uses a column filled with tiny particles. A liquid sample is injected into the column using a high-pressure pump. As the sample passes through the column, components in the sample appear, or “elute”, at different time points, known as retention times. A detector shines UV light through the column, generating signals that register as peaks on a graph, corresponding to each component. These peaks are compared to peaks generated by a reference standard sample of the tested substance. The column is referred to as the stationary phase, while the solvent that carries the sample through the column is called the mobile phase.

TLC (Thin-Layer Chromatography)

TLC is a chromatographic technique that uses a thin plate made of metal, plastic or glass, coated with a thin layer of silica or aluminum as the stationary phase. A solution of the sample is mixed with a solvent (the mobile phase), and applied to the bottom of the plate. As the sample migrates up the plate via capillary action, its various components travel at different rates. The plate is then developed, producing a chromatogram with horizontal bands corresponding to the components. A TLC chromatogram can in many cases provide a fingerprint that is more visually distinct than an HPLC read-out. Multiple TLC chromatograms

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can be compared side-side for comparative visual analysis. For these reasons TLC is a practical and efficient analytical technique, especially for botanicals, which have species-specific chromatographic fingerprints.

GC (Gas Chromatography)

Gas chromatography is used to analyze volatile organic substances. The mobile phase consists of a vaporized sample carried by an inert gas such as helium. As the sample travels through the stationary phase, compounds in the sample elute at specific retention times and appear as peaks on the chromatogram, as in HPLC.

FT-IR (Fourier Transform Infrared Spectroscopy)

Infrared spectroscopy measures the effects of infrared light on the vibration of molecules in organic and inorganic substances. The chemical bonds in a molecule bend and stretch as they absorb infrared light at specific wavelengths. FT-IR uses infrared light to characterize this absorption spectrum as a unique molecular "fingerprint" for a particular substance. Once a standard FT-IR fingerprint for an ingredient is established, this technique can be an efficient way to perform identity testing. For multi-ingredient products, finished product batches that conform to specifications, as verified by other analytical tests, may be used to create a

product fingerprint against which batch-to-batch quality testing can be conducted.

MS (Mass Spectrometry)

Mass spectrometry detects and analyzes organic and inorganic compounds at very low concentrations in a sample. The analytical instrument—the mass spectrometer—splits molecules into ionized (electrically charged) fragments. By measuring the mass-to-charge ratio of an ion, the molecular weight and chemical structure of the parent molecule is determined. Mass spectrometry may be utilized in combination with liquid and gas chromatography. This approach is particularly useful for compounds present in a sample at levels too low to be detected chromatographically.

In summary, the cGMP Final Rule for dietary supplements is a mandate for product quality. Authenticating the identity of dietary ingredients, as well as confirming conformance of finished product batch to specifications, must be ongoing. In order to yield scientifically valid results that will pass muster in an FDA inspection, analytical lab operations must be conducted according cGMP standards. Achieving and maintaining compliance with cGMP requires dietary supplement manufacturers to build robust analytical testing plans into the product development, manufacturing and quality control processes.

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