REVIEW ARTICLE JPAR 2018

Journal of Pharmaceutical Advanced Research
(An International Multidisciplinary Peer Review Open Access monthly Journal)
Available online at: www.jparonline.com

Overall Role of GMP Requirements in Dietary Supplement Production

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Received: 25.10.2018 Revised: 27.10.2018 Accepted: 29.10.2018 Published: 31.10.2018

ABSTRACT: A good manufacturing practice (GMP) is one that ensures the guidelines set by the regulatory organizations that control approval and authorizing for the production and market the food, beverages and various pharmaceutical products including dietary supplements. Dietary supplement" implies an item marketed under food law, containing at least one or more dietary element in a concentrated form, which may likewise contain various other ingredients, displayed in a form designed for single or numerous dose administration, including however not restricted to tablets, capsules, powders or fluids. The Dietary Supplement Good Manufacturing Practice (DS GMP) regulations are basically about a method for accomplishing reliable quality in items made.

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Keywords: GMP, Dietary Supplement, cGMP (Current Good Manufacturing Process).

INTRODUCTIONS:

In 1905, a book called The Jungle helped catalyze public opinion for change. Muckraker and social reformer Upton Sinclair expounded on the Chicago meat packaging industry—the unsanitary conditions in which various animals were slaughtered and processed and the act of selling rotten or diseased meat to the general society. He additionally detailed about ground meat sometimes contained remains of diseased rats and even unfortunate workers who fell into the machinery. Sinclair's fundamental interest was in focusing on the miserable working conditions and the plight of the

impoverished factory workers, a large number of them were immigrants [1].

The Pure Food and Drug Act:

Congress passed the Pure Food and Drug Act in 1906, and for the first time ever it became unlawful to market contaminated (adulterated) food or meat. Likewise for the first time, labeling had to be correct - no longer could anyone be able to guarantee the label "the moon and the stars". 1906 Act additionally required selected dangerous ingredients to be named on all drugs. Inaccurate or false labeling was called misbranding, and that became illicit. "Misbranded" applies to proclamations, plans, or pictures in labeling that are false or misleading and additionally to the inability to give required data in labeling. A 1933 FDA exhibit of dangerous food, medicines, medical devices, and cosmetics illustrated the shortcomings of the 1906 law.

In 1980, Congress passed the Infant Formula Act giving FDA authority to create and enforce standards and specify nutritional requirements for commercial infantformulas.FDA issued tamper-resistant packaging regulations for all over-the-counter human drug products and incorporated them into the GMPs. Congress passed the Federal Anti-Tampering Act in 1983, making it a crime to tamper with packaged consumer products [2].

Guidance Document:

In the 1980s, FDA started distributing a progression of guidance documents that had majorly affected our translation of current good manufacturing practices. One such record was the 1983 "Guide to Inspection of Computerized Systems in Drug Processing," which gave early desires for the working of computer systems and may be flagged the start of computer validation [3].

Various resources of GMP:

- ***United States (U.S.): Food and Drug Administration (FDA)*:** In1978 CGMPs were issued, a draft version was released and comments from the industry were requested. These comments and FDA's responses were published in the "Preamble" to the CGMPs.
- ***Australia: Therapeutic Goods Administration (TGA)*:** Australian Code of Good Manufacturing Practice for Medicinal Products
- ***Canada: Health Canada* :** Good Manufacturing Practice (GMP) and guidance documents
- ***Europe: European Medicines:*** Volume 4 Medicinal Products for human and veterinary use: Good Manufacturing Practice and related Annexes and Glossary.

GOOD MANUFACTURING PRACTICES (GMP's) FOR DIETARY SUPPLEMENTS:

Dietary supplement means a product marketed under food law, containing one or more dietary ingredients in a concentrated form, which may also contain other ingredients, presented in a form intended for single or multiple dose administration, including but not limited to tablets, capsules, powders or liquids.

Dietary supplements are products that people add to their diets. They include vitamins, minerals, herbs, and other substances. Dietary supplements are meant to improve your diet. They can come as pills, capsules, powders and liquids. Dietary supplements may even come in drinks or energy bars. Dietary supplements can play an important role in health. However, supplements shouldn't replace the variety of foods that are important to a healthy diet. People use dietary supplements for a wide variety of reasons. Some people use supplements to boost energy or get a good night's sleep [4].

The Hidden Dangers of Dietary Supplements:

Not all supplements are effective. There are tens of thousands of supplements sold in the US, and while some are very effective, many are not. Even worse, some might actually cause more harm than good. Little is known about the safety of supplements, because Congress requires that the US Food and Drug Administration (FDA) assume that all supplements are harmless until proven otherwise. Because the government does not ensure supplement safety, it's especially important that consumers are careful when purchasing supplements [4].

Tips for safe use of supplements:

- The best way to use supplements safely is to avoid supplements you don't need. Use supplements only if you have reliable information that the ingredient(s) will benefit you. Accurate information can be found at the National Institute of Health's National Center for Complementary and Alternative Medicine.
- Select supplements with only the ingredient(s) that you need. If you need vitamin D then select a supplement that only contains vitamin D.
- Avoid supplements with more than one herbal ingredient. It is very difficult to determine the effect that multiple herbs will have on your health.

- If you take prescription medications or have health conditions, ask your physician if the supplement you are considering is safe for you.
- Avoid supplements that are sold to treat an illness, for example supplements sold to treat diabetes, high blood pressure, or high cholesterol. These supplements are more likely to be contaminated with prescription medications.
- Avoid supplements that claim to help you lose weight or improve sexual or athletic performance. These supplements may not only be contaminated with prescription medicines but also with dangerous analogs.
- If you experience a side effect from a supplement: Stop using the supplement, inform your physician, and inform the FDA [5].

Dietary Supplements- CGMP Requirements for Quality Control:

New regulations for Dietary Supplement manufacturers require a Quality Control (QC) function to oversee manufacturing and packaging operations. QC personnel are expected to ensure the quality of the dietary supplement a manufacturer makes as well as the correct packaging and labeling as specified in the master-manufacturing record. In this role, QC must approve or reject factors affecting the identity, purity, strength or composition of a dietary supplement. This includes processes, specifications, written procedures, controls, tests and examinations as well as any deviations – from or modifications to – an operation. In this course, you will be able to identify regulatory requirements for quality control operations, including material review and dispositions, laboratory operations, product complaints, returned products and other process control operations.

It consists of Roles of quality control, Laboratory operations, Material reviews and dispositions, Returned products, Product complaints, Review and approval of manufacturing equipment, Master and batch record approvals, Packaging and labeling oversight and Procedures and records maintenance [6].

GMP FOR DIETARY SUPPLEMENTS:

Food GMP Compliance:

In addition to the requirements stated below, all applicable food GMP standards, including those related to Qualifications and hygienic practices related to personnel and The design, construction, maintenance and sanitation of buildings, facilities, equipment, utensils, dietary products and other ingredients, shall be followed in the manufacturing of dietary supplements [7].

Hazard Analysis and Critical Control Points (HACCP):

The principles of Hazard Analysis and Critical Control Points (HACCP) shall be observed in the manufacturing of dietary supplements. This shall include the identification of any step in their activities which is critical to ensuring food safety and ensure that adequate safety procedures are identified, implemented, maintained and reviewed in accordance with the following HACCP principles [8]:

- Analysing the potential food hazards in a food business operation.
- Identifying the points in those operations where food hazards may occur.
- Deciding which of the points identified are critical to food safety - the critical points.
- Identifying and implementing effective control and monitoring procedures at those critical points.
- Reviewing the analysis of food hazards, the critical control points and the control and monitoring.
- Procedures periodically and whenever the food business operations change.

Quality Assurance, Quality Control and Laboratory Operations:

Appropriate quality control operations and/or Quality Assurance activities shall be employed to assure that dietary products conform to appropriate standards of purity, quality, composition and claimed label content, and that packaging materials are safe and suitable for their intended purpose.

It should consist of Quality Control Unit, Laboratory records, Best Before/Expiration dating and Self – Inspections [9].

Production and Process Controls:

It consist of following (a) Master production and control records, (b) Batch production and control records, (c) Handling, storage and testing of raw materials, in-process materials and rework, (d) Manufacturing operations and (e) Packaging and labeling operations [10].

Warehousing, Distribution and Post-Distribution Procedures [10-14]:

Storage and distribution:

Storage and transportation of finished product shall be under conditions that will protect product against

physical, chemical, and microbial adulteration as well as against deterioration of the product and the container.

Adequate distribution records shall be maintained and retained by the manufacturer at least one year beyond expected product shelf life, or designated "best before" or expiration date, whereby an effective product recall can be achieved should one become necessary.

Reserve samples:

An appropriately identified reserve sample that is representative of each batch of a dietary product should be retained and stored under conditions consistent with the product labeling until at least one year after the "best before" or expiration date, or if no such date is identified on the product, for at least three years after the date of manufacture.

Records retention:

Any laboratory, production, control or distribution record specifically associated with a batch of product shall be retained for at least one year after the "best before" or expiration date of the batch, or if no such date is identified on the product, for at least three years after the date of manufacture.

Raw material records shall be maintained for at least one year after the "best before" or expiration date of the last batch of product incorporating the raw material, or if no such date is identified on the product, for at least three years after the date of manufacture of the finished product.

Complaint files:

A written record of each complaint shall be maintained, until at least 1 year after the "best before" or expiration date of the product, or 1 year after the date that the complaint was received, whichever is longer.

The written record shall include, where known: the name and description of the product, lot number, "best before" or expiration date, name of complainant, nature of complaint, and reply to complainant, if any.

Where an investigation is conducted, the written record shall include the findings of the investigation and follow-up action taken.

Returned products:

Returned dietary products shall be identified as such and held. If the conditions under which returned dietary products have been held, stored, or shipped before or during their return, or if the condition of the product, its container, carton, or labeling as a result of storage or shipping, casts doubt on the purity, quality, composition or claimed label content of the product, the returned product shall be destroyed unless examination, testing or other investigations prove the product meets appropriate standards of purity, quality, composition and claimed label content.

If the tamper-evident seal of a returned product is broken, it should be destroyed and not reprocessed. A product may be reprocessed provided the subsequent product meets appropriate specifications.

Product salvaging:

Dietary products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace.

Contract Manufacturing:

Whenever a contract manufacturer performs any portion of product manufacturing, the responsibilities of the contract manufacturer concerning the accomplishment of GMP functions shall be documented.

Pharmaceutical Validation [14,15]:

Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale.

Lending importance to validation is increasingly profound in recent years. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials.

Process validation:

It can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes (ICH Q7).

Continuous process validation:

It has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. This approach is based on the knowledge from product and process

development studies and or previous manufacturing experience.

Process validation:

It should not be viewed as a one-off event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

DISEASES CAUSED DUE TO DEFICIENCY OF VARIOUS DIETARY SUPPLEMENT [16-19]:

Infant reflux:

It occurs when food backs up (refluxes) from a baby's stomach, causing the baby to spit up. Sometimes called gastroesophageal reflux (GER), the condition is rarely serious and becomes less common as a baby gets older. It's unusual for infant reflux to continue after age 18 months.

Scurvy:

It is a disease caused by a diet that lacks vitamin C (ascorbic acid). Patients develop anemia, debility, exhaustion, edema (swelling) in some parts of the body, and sometimes ulceration of the gums and loss of teeth.

Beriberi:

It is a disease caused by a vitamin B1 (thiamine) deficiency. There are two types of the disease: wet beriberi and dry beriberi. Wet beriberi affects the heart and circulatory system. In extreme cases, wet beriberi can cause heart failure. Dry beriberi damages the nerves and can lead to a loss of muscle strength and eventually, muscle paralysis. Beriberi can be life-threatening if it isn't treated.

Rickets:

It is a skeletal disorder that results from a lack of vitamin D, calcium, or phosphate. These nutrients are important for the development of strong, healthy bones. People with rickets can have weak and soft bones, stunted growth, and, in severe cases, skeletal deformities.

Pellagra:

It is a disease that occurs when a person does not get enough niacin (one of the B complex vitamins) or tryptophan (an amino acid). Pellagra is caused by having too little niacin or tryptophan in the diet.

Marasmus:

It is an extremely severe type of nutrition disorder in which there is significant wasting of fats, muscles, and tissues of the body. Marasmus is considered as one of the serious types of malnutrition across the globe.

Kwashiorkor:

It also known as "edematous malnutrition" because of its association with edema (fluid retention), is a nutritional disorder most often seen in regions experiencing famine. It is a form of malnutrition caused by a lack of protein in the diet.

PHARMACEUTICAL APPROACHES IN DIETARY SUPPLEMENT:

Revital:

Revital' – one of the India's leading daily- nutrition supplement products. It is one such product in the wide array of health products that are available today. Growing number of consumers prefer to use such products for reasons like; to combat stress and the high tension environment at workplaces, to compensate for their 'junk food' diet, to maintain and retain their energy levels in today's fast paced life, to avoid / prevent falling sick, to retain mental alertness and focus and to improve general immunity level and health

Glucon D:

Glucon D, the so called instant energy drink specially made for summers. It is a glucose based beverage known for its quick absorption and gives instant energy. Unlike other energy drinks, it doesn't contain any caffeine or any other chemical that may affect the body.

Protein X:

Many people take protein powders in an effort to gain muscle. However, there is some controversy as to whether this is really effective. There is evidence suggesting that consuming high level s of protein may in fact have negative side effects for your health. It is certainly true that protein required building muscle, as well as for numerous other important functions in the body. However, there is a limit to how much muscle growth can actually occur, no matter how much protein you consume.

Calcium Sandoz:

This medication is a dietary supplement, prescribed for calcium deficiency state which may occur in diseases such as decreased levels of parathyroid hormone (acute and chronic), postmenopausal osteoporosis, rickets and osteomalacia (softening of the bones). It is also used as an antacid.

Yakult:

Yakult is a delicious probiotic fermented milk drink that contains Yakult's exclusive probiotic LcS *(L. casei strain Shirota)*. Daily consumption of Yakult helps improve digestion and helps build immunity**.**

CASE STUDY:

A 27-year-old Nigerian student actuary was admitted on 8 December 1966. He had come to England from Lagos in 1959. He complained of painful swelling of the right calf and to a lesser extent of the left calf of 3 weeks' duration. He was a marathon runner of international standard and trained by running 30 miles a day. He had been able to carry out his daily training until 5 weeks before admission when he had first noticed excessive shortness of breath during exercise. For 2 years his gums had been swollen and had sometimes bled. He was unmarried and cooked for himself. He had never eaten fruit or fresh vegetables. On examination, he was a fit-looking man, although with marked pallor of the mucous membranes. He was not jaundiced. There were multiple splinter hemorrhages under all the finger nails, which were otherwise normal. The skin was normal. The gums were hypertrophied with areas of bleeding. There were petechiae on the palate. The right calf was swollen and tender with slight pitting oedema at the ankle. Homan's sign was positive. The left calf was also swollen and tender. There were no other abnormal physical signs. Hess' test was negative.

DISCUSSION:

The anemia of scurvy is probably due to several factors that are extracorpuscular haemolysis, extravasation of blood, relative lack of folinic acid, dyshaemopoiesis and associated dietary deficiencies. The first four are reversible with vitamin C alone. In our patient the anaemia was normochromnc and normocytic, and responded to vitamin C, bed rest and routine hospital diet. The case is remarkable in that the disease presented with anemia, the only other clinical manifestation of scurvy being bleeding from the gums. There was none of the other manifestations of scurvy such as hyperkeratosis, perifollicular haemorrhages or subcutaneous purpura. The case is unusual in that there was no evidence of other dietary deficiency such as folic acid or other vitamins.

CONCLUSION:

The FDA is concerned about the quality of dietary supplements in the United States. There is little product reliability, and because patent protection is not available for natural products, there is little incentive for manufacturers to invest resources in improving product standardization. In addition to the confusion that this introduces to consumers, the lack of reliable and consistent products is a challenge to the research and clinical practice communities. Without consistent products, research is extremely difficult to conduct or generalize. Furthermore, without high-quality research, evidence-based clinical recommendations cannot be made to guide patients.

As a result of their pharmacological properties, dietary supplements, particularly botanical products, carry a risk of adverse effects and interactions. Unlike vitamins and minerals, herbal supplements are composed of many active compounds, and often, the primary active ingredient is unknown. Without knowing the active ingredient(s), it is a challenge for manufacturers to set standards that bear any therapeutic meaning. As such, consistency and quality checks throughout the manufacturing process garner even more importance.

To improve product consistency and reliability, the committee recommends that the U.S. Congress and federal agencies, in consultation with industry, research scientists, consumers, and other stakeholders, amend the Dietary Supplement Health and Education Act of 1994 and the current regulatory scheme for dietary supplements, with emphasis on strengthening: Seed-to-shelf quality control, Accuracy and comprehensiveness in labeling and other disclosures, Enforcement efforts against inaccurate and misleading claims, Research into how consumers use supplements, Incentives for privately funded research into the efficacies of products and brands, and Consumer protection against all potential hazards.

The conclusion from the available data (new and old) is that consumption of dietary supplements for prolonged periods appears not to be safe and is not cost-effective in primary prevention of chronic disease. Practitioners should evaluate each case individually and take a decision based on available evidence-based data when considering dietary supplements in this population.

ACKNOWLEDGEMENT:

Authors wish to thanks the Authority of Shri Ram Murti Smarak College of Engineering and Technology (Department of Pharmacy), Bareilly, for providing library and other facilities to complete successfully this review study.

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Conflict of Interest: None

Source of Funding: Nil

Paper Citation: Akhtar MS, Agarwal P. Overall Role of GMP Requirements in Dietary Supplement Production. J Pharm Adv Res, 2018; 1(8): 355-361.