NIH Office of Dietary Supplements
Panel Presentation
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Nutramax Laboratories, Inc. was founded in 1992 and developed the first Glucosamine/Chondroitin Sulfate product and still the only brand backed by published U.S. clinical studies. We have sales domestically as well as internationally and Cosamin® is the number one glucosamine/chondroitin sulfate brand recommended by Orthopedic Surgeons and Rheumatologists[1]. We are a privately held, Christian-based company located in Edgewood, MD with approximately 105,000 square feet of factory, laboratory, warehouse and office space. Our mission is to provide safe, effective, high quality nutritional health products that support the active lifestyles of people and animals. We seek to meet this objective through Research & Development of our products. Currently we maintain an intellectual property portfolio that includes several patents, many including claims related to dietary supplement ingredients. We have invested over $14 million in Manufacturing and Quality Compliance equipment to maintain what we believe are the highest standards practiced today in the dietary supplement industry. Marketing and sales of our products are largely handled by internal organizations, although we also have relationships with several national distributors and brokers.

At present Nutramax Laboratories, Inc. employs approximately 210 employees. Within these ranks we employ 13 individuals with doctorate level degrees, 12 employees with Master degrees and 41 employees with Bachelor degrees. Many of our employees have extensive experience in the pharmaceutical industry, including our 31 employees in Quality Compliance and the 72 people employed in Manufacturing Operations.

Most of our product manufacturing is performed at our Edgewood, Maryland location in a Class 100,000 environmentally controlled facility. This production environment includes HEPA-filtered air, humidity control in a positive pressure "bubble" with air locks to prevent the ingress of contaminants. All of our manufacturing employees have extensive SOP training as well as cross training on multiple pieces of manufacturing equipment. In addition, all of our manufacturing employees are given routine Good Manufacturing Practice (GMP) training and safety training on an on-going basis throughout the year.

Quality is a State of Mind – an Ongoing Process of Improvement

Position on cGMP Regs

Nutramax Laboratories, Inc. supports strong current Good Manufacturing Practices (cGMPs) to ensure that dietary supplement products are not adulterated with contaminants or impurities, and are labeled accurately. As such we support, and we believe we exceed the Dietary Supplement GMPs issued recently by the FDA. By way of comparison the most significant differences between Dietary Supplement GMPs and Pharmaceutical GMPs are in the areas of Validation and Stability/Expiration Dating concepts. At Nutramax Laboratories, Inc., we basically follow the manufacturing standards practices by the pharmaceutical industry. In February 2006, the FDA conducted a routine inspection of our manufacturing operations that yielded no 483's, no deficiencies, and in the inspector's final report even acknowledged that we use "drug GMPs" in the manufacturing of our dietary supplements.

To further bolster our philosophy of quality, we are currently implementing a paperless batch record system. In addition, Nutramax Laboratories, Inc. fully complies with the new requirement for mandatory reporting of serious AERs for consumer dietary supplements that went into effect in December 2007. The effort required to comply with the new AER law was truly minimal since we already had a system in place prior to this requirement.

Evidence Based Studies

Nutramax Laboratories, Inc. is committed to sound science in the development of our products. Many of the studies were done independently (we only supplied intervention and/or placebo) by Universities as well as the US Department of Defense. We have numerous published studies on our products many published in recognized journals including

Osteoarthritis and Cartilage
Biopharmaceutics and Drug Disposition
Clinical Orthopedics and Related Research
Society for Experimental Biology and Medicine
Archives of Internal Medicine
American Journal of Veterinary Research
Journal of Rheumatology
Military Medicine

Just in the last 24 months, we have presented several abstracts and poster presentations at various U.S. and International venues such as:

ICRS (International Cartilage Research Society)

OARSI (Osteoarthritis Research Society International)
ORS (Orthopedic Research Society)
World Biomaterials Congress in Amsterdam

To support scientific education, we have established a basic science research internship program that covers studies in both human and veterinary medicine. Over the last three years, we have trained multiple students, residents, and fellows through this program.

None of this happens by accident; before we perform a study we do our homework. We begin with an extensive literature search for safety and efficacy on the material we are considering. Our scientists evaluate the published literature before we proceed. Once we decide to proceed with initial development, we obtain sample material and determine if the supplier meets our commitment to manufacturing quality. If satisfied on these issues, our Quality Assurance department begins the supplier audit process.

Quality Assurance

Auditing Suppliers, Laboratories, and Contract Manufacturers

At Nutramax Laboratories, Inc., we have a fully staffed Quality Assurance (QA) department. On the QA team there is a Supplier Quality Engineer (SQE) who is responsible for coordinating both internal audits as well as external audits of our suppliers, labs and contract manufacturers that we use. Internally, the SQE will audit multiple times throughout the calendar year pursuant to 21 Code of Federal Regulations (CFR), Part 211, Finished Pharmaceutical Good Manufacturing Practices (GMPs).

In addition to the internal audits, we conduct routine periodic external audits of our distributors and suppliers of our active and inactive raw materials, laboratories as well as a few off-shore manufacturers licensed to make our products for overseas markets.

There are approximately 8 Nutramax Laboratories, Inc. personnel qualified to conduct these audits including the SQE. These individuals, including the SQE, have between 5-30 years experience in the pharmaceutical industry.

We are very proud of the priority and focus we give this part of the business. It is critically and frankly vital to our long term business interests that our ingredients meet our high standards of quality; that laboratories used in the testing of our products deliver validated results; and that production facilities used for our products practice sound GMPs to meet our customers' expectations for our products.

Analytical Chemistry

The goal of Analytical Chemistry (AC) is to develop assays for new products, validate the methods and transfer them to our QC lab once the assay development is completed. The goal of the QC lab is to take those developed, validated and transferred methods and

run them routinely to test and release raw materials and final products used and manufactured or packaged by Nutramax Laboratories, Inc.

The AC Lab is currently comprised of scientists all have either a Ph.D. in Analytical Chemistry, Masters Degrees; or Bachelors Degree in the science field.

The AC Lab is outfitted with state-of-the-art analytical instrumentation including several Gas Chromatograms (GCs), a GC-Mass Spectrophotometer (MS), Inductively Coupled Plasmospectroscopy (ICP), several High Liquid Performance Chromatography (HPLCs) and Ultra Liquid Performance Chromatography (UPLC) units. Other instrumentation equipment includes centrifuges, a particle size analyzer (PSA), microbalances, balances, and pH meters.

The AC scientists are responsible for the development of methods and sample extraction techniques. Once the methods of sample prep and the assay are developed, these methods go through validation. The validation of the assays allows us to establish specification and ranges with the variability of the assay methodology included for each active in the raw and finished forms. Once methods are validated and specifications are established by the AC group, they are transferred to the QC lab. This is done under a formal protocol, using a scientist from the AC lab and an analyst in the QC lab.

Stability

In addition to assay development, validation and transfer, the AC lab performs a critical function to new product development in the area of stability. The AC lab has a stability program for marketed products including new products under development. The stability program runs protocols and studies in accordance with the International Conference on Harmonization (ICH) and FDA guidelines. Running these protocols at various temperatures and conditions helps us understand the long term stability and shelf life of our products.

Quality Control

QC tests products on stability for the stability group. They also test raw materials and test final products before they are sold to the public. Some tests are sent out to qualified outside laboratories.

As a part of our continuous improvement initiatives, the QC lab is currently evaluating systems to improve throughput and efficiency such as the following:

- Selection and implementation of a Laboratory Information System (LIMS).
- Implementation of a Rapid Micro testing scheme; and a more fully developed, in house environmental monitoring (EM) program to supplement our existing program.

How Nutramax Laboratories, Inc. Utilizes Scientific Research for Evaluating and Developing Dietary Supplement Health Products

The first step in product development is pre-clinical screening using *in vitro* tissue cell-based models down to molecular level. These models examine cellular response to the test agent that could help predict the response in the body. They also provide information on how the agent may work and their potential mode of action. The dose response obtained *in vitro* also provides direction to range of doses in *vivo.* At Nutramax Laboratories, Inc. we follow a very similar screening approach to select the active ingredients or materials that will form the basis of our new product developments.

Research and Development

The Nutramax Laboratories, Inc. R&D Department is headed by Dr. Carmelita G. Frondoza. Dr. Frondoza was granted her Ph.D. in Immunology from the Johns Hopkins University (JHU). She had served for 12 years as Johns Hopkins Orthopaedics Research Director of Arthritis Surgery prior to coming to Nutramax Laboratories, Inc. She continues to maintain a part time appointment as associate professor at Johns Hopkins University and an adjunct professorship at Mississippi State College of Veterinary Medicine. The R&D team is composed of Bioengineers, cell and molecular biologists. Our R&D supervisor, who reports to Dr. Frondoza, has a Master's degree in Bioengineering and is currently completing her Ph.D.

To evaluate new raw materials we use consensus scientific methods. We test our products on tissue cell models that are the structural units of organs in the body. Examples are cells from cartilage, bone, tendon, ligament, synovium, immune system and liver. To visualize the cells and what they produce, we use microscopy and protein chemistry. We also measure what these tissue cells models are capable of producing using molecular biology techniques such as real time polymerase chain reaction.

Then are we ready to begin veterinary clinical trials followed by human if applicable. Once on the market we continue not only to monitor suspected adverse events, but address any concerns by physicians.

Example with Cosamin®DS

- Since Glucosamine is a Glucose-like molecule, how does it effect glycemic control in patients with type 2 diabetes mellitus? This fear was alleviated by an independent study published in Annals of Internal Medicine.

- Another concern was whether Chondroitin Sulfate alters prothrombin time which was again looked at in another independent clinical study published in Military Medicine .

Often Dietary Supplement (DS) materials are more difficult to study than pure chemicals. DS studies may fail for the following reasons:

1. Poor design including outcome measures, population group, and improper dosing.
2. Not understanding how the material works at the molecular level.
3. The use of assay methods that are not fully validated for the product being studied.
4. Lack of bioavailability data.

The selection of a reputable investigator respected by his/her peers and one that is not biased against Dietary Supplements and does not receive "Big Pharma" grants and consulting fees is essential.

Let me cite two recent, personal examples of difficulties encountered with dietary supplement clinical studies:

1. We had an IRB approved study underway and patient enrollment had begun. The study was discontinued because the investigators could not enroll enough patients for our study because they were given a large grant to study a drug in the same patient population. The investigators and research hospital involved were attracted by the larger funding and prestige of the pharmaceutical study and our study was placed on hold.
2. The recent NIH $16 million funded Glucosamine/Chondroitin Sulfate Arthritis Intervention Trial (GAIT) for painful knee OA in which Nutramax Laboratories, Inc. (as well as it's chondroitin sulfate manufacturer) supplied the chondroitin sulfate material used in the study, was performed by a number of experts who had potential conflicts of interest as acknowledged in the NEJM[2] page 807. Some of these experts when addressing the media played down the fact that the combination of Glucosamine Hydrochloride (HCl) and Chondroitin Sulfate was effective in moderate to severe knee pain due to OA. The first abstract presented on the data stated that the glucosamine plus chondroitin sulfate **is effective** in treating moderate to severe knee pain due to OA. The lack of response in patients with mild pain may be due to a floor effect, limiting ability to detect response. All study agents were well tolerated. The actual publication in the NEJM stated that an exploratory analysis suggest that the combination of glucosamine and chondroitin sulfate **may be effective** in the subgroup of patients with moderate to severe knee pain. The message that a supplement may be an option for patients with knee pain continued to get watered down.

With these kinds of obstacles to overcome, it is no wonder most of the Dietary Supplement companies would rather market to consumers with advertising than devote their resources to peer reviewed publishable clinical studies. With proper incentives and a level playing field, I believe more Dietary Supplement companies would devote the resources needed to conduct meaningful research. In conclusion I would like to suggest that before the NIH Office of Dietary Supplements awards any research grants for

Dietary Supplement research, they examine the existence of any conflict of interest of all investigators so that unbiased results can be reported.

References:

[1] Source: SLACK Incorporated Market Research Survey, June 2005 and February 2006. Surveys conducted of orthopedic surgeons and rheumatologists relating to glucosamine/chondroitin sulfate brands.

[2] Clegg DO, et al. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. N Engl J Med. 2006;354:795-808.