Insights on FDA Enforcement Activities: Corrective Actions & Dealing with FDA Post Inspection; New FSMA Requirements for

NIA 2012 Forum
May 31, 2012
April 10, 2012: Founder of Bodybuilding.com Pleads Guilty to Selling Misbranded Drugs as Dietary Supplements

BOISE – Bodybuilding.com founder and CEO Ryan DeLuca, 34, of Eagle, Idaho, pled guilty yesterday in federal court in Boise to five misdemeanor counts of introduction and delivery for introduction of misbranded drugs into interstate commerce, U.S. Attorney Wendy J. Olson announced. The five charges are all violations of the Food, Drug and Cosmetic Act. As part of the plea, DeLuca agreed to pay a $500,000 fine. The United States agreed to recommend that DeLuca receive probation and not be sentenced to any prison term.
January 17, 2012: Two Manufacturers Sentenced for Misbranding Products as Dietary Supplements

The companies pled guilty in November 2011. According to the plea agreements, DCD, LLC dba Advanced Muscle Science (DCD), and R&D Holdings, LLC dba Culver Concepts, Bradley Asgard, and Bjorklund (R&D Holdings), misbranded products as dietary supplements, when the products were actually drugs, as defined under the Food, Drug and Cosmetic Act (FDCA) and the Dietary Supplement Health and Education Act (DSHEA). The charges were brought in federal court in Idaho because the companies delivered their products to a retail company located in Idaho for further distribution throughout the United States.
U.S. Department of Justice Press Release
November 9, 2011: Supplement Manufacturers Plead Guilty to Selling Products Containing Unapproved Drugs

According to the Information, Axis Labs engaged in the business of manufacturing, labeling, shipping and selling certain food products. The business was active in and responsible for the distribution and marketing of a product called “Monster Caps.” The intended use of the product was to enable weight loss and the production of muscle mass. The product falsely purported pursuant to its label to be a “dietary supplement” and therefore could be distributed and dispensed without prior approval from the FDA and without a prescription from a duly authorized physician.
U.S. Department of Justice Press Release:
May 5, 2011: Dietary Supplements Manufacturer Sentenced

According to the plea agreement, Tribravus / IForce distributed the products “17aPheraFLEX,” “Dymethazine” and “Methadrol” as dietary supplements. The FDA found that these products contained synthetic steroids, known as “DMT” or “Madol” and “Superdrol.” Thus they were not dietary supplements but rather unapproved drugs under the Food, Drug and Cosmetic Act. Tribravus Enterprises agreed to pay the $125,000 fine and implement a testing protocol for its products to ensure future products sold as dietary supplements do not contain synthetic steroids.
Dietary Supplement Products Spiked with APIs

400 products since 2008
DS Adulterated w/APIs 2010 and 2011

2010

• Men’s Virility
  • 17 recalls (76 products)

• Diet / Weight
  • 6 recalls (7 products)

• Sports Nutrition
  • 2 recalls (18 products)

2011

• Men’s Virility
  • 10 recalls (15 products)

• Diet / Weight
  • 5 recalls (17 products)
Inspection Activity by Year

2008 – 7 Inspections (7/25/08 – 9/30/08)
2009 – 34 Inspections
2010 – 84 Inspections
2011 – 145 Inspections
2012 – Already 138 Inspections as of 5/8/12

FDA estimates a 30-40% non-compliance rate had deficiencies noted on 483s & Warning Letters
FDA estimates a 30-40% non-compliance rate (had deficiencies noted on 483s & Warning Letters)
FDA issued its first warning letter for dietary supplement GMP violations on March 30, 2010. There have been more than 70 additional warning letters since that time.
GMP Inspectional activities include (but are not limited to):

1) General facilities
2) Component specifications
3) Dietary ingredient identity testing and component identity confirmation
4) Master manufacturing records and product specifications
5) Manufacturing processes and batch production records
6) Complaints & adverse events reporting
7) Quality control oversight (review & release of finished batch)
8) Ingredient and finished product specifications and release criteria
9) Testing of finished dietary supplement batches
Recent Inspection Findings

**Master Manufacturing Records**
- Missing
- Lack of required components
- Lack of details about process

**Batch Production Records**
- Missing
- Missing required components
- Missing recorded details about completed activities

**Specifications**
- Failure to establish specifications (RM & FP)
- Failure to determine if specifications are met (RM & FP)
Recent Inspection Findings

Quality Control

• Failure to provide adequate oversight
• Failure to review and release BPR
• Releasing batches that do not meet specifications

Contract Manufacturers

• Lack of finished product testing
• Releasing batches before testing is complete
• Not qualifying suppliers (using C of A results)
Recent Inspection Findings

Own Label Distributors

- Failure to set specifications
- Failure to provide oversight of CMs
- Failure to ensure specifications are met prior to introduction into interstate commerce

Product Complaints

- Failure to submit SAERs to FDA
- Failure to keep written records of complaints
- Failure to investigate GMP related complaints
Review of product complaint system is receiving much more attention from Inspectors in recent inspections

- FDA believes there is under reporting in the industry
  - 1119 SAER in 2008
  - 1306 SAER in 2009
  - 1395 SAER in 2010
  - 2473 SAER in 2011
  - FDA Predicts 14,000 in 2014

- FDA expecting analysis of incident rates by age and outcome
Review of product complaint system is receiving much more attention from Inspectors in recent inspections cont.

- Know the incidence rate of predicable outcomes (i.e. niacin flush – so that a change would be a cause for concern)
- Define your system for evaluating SAERs – causal, associative
- Enhanced surveillance start to look for – long term effects due to chronic use, changes in consumption patterns leading to use of product unlike original intent – (i.e. energy products, events due to interactions)
- Some companies have been providing FDA’s phone number for AER reporting (misbranded)
- Must make and keep a written record of every complaint related to a “possible” failure to meet GMPs
“GMPs (are) the biggest challenge...facing the dietary supplement industry, at least that’s the way the regulators see it, and we hope everyone understands that.”

- Dr. Daniel Fabricant
A food shall be considered adulterated.....If it is a dietary supplement that has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations......Section 402(g)(1), Federal Food, Drug, and Cosmetic Act
Inspectional Observations by Subpart

- K - Manufacturing Operations: 3%
- M - Holding & Distribution: 3%
- N - Returns: 1%
- O - Product Complaints: 4%
- P - Records: 1%
- Q - Packaging & Labeling Operations: 4%
- B - Personnel: 5%
- C - Physical Plant & Grounds: 12%
- D - Equipment & Utensils: 6%
- E - Production & Process Controls: 16%
- F - Quality Control: 12%
- G - Components (packaging/labels): 8%
- H - MMR: 8%
- I - Batch Records: 9%
Subpart E Warning Letters by Topic

- Specifications: 37%
- Finished Product Testing: 20%
- Identity: 17%
- Sampling: 17%
- Supplier Qualification: 17%
- Material review: 2%
Under what authority does FDA issue 483s?

1) “The observations of objectionable conditions and practices listed on the front of this form are reported:
   
   A. Pursuant to Section 704(b) of the FFD&C Act
   B. To assist firms inspected in complying with the Acts and regulations enforced by the FDA”
483 Observations

• “This document lists observations made by the FDA representative during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance.”

(Form FDA 483 & FDA Investigations Operations Manual (IOM) 5.2.3.1.4 http://www.fda.gov/ora/inspect_ref/iom/)
FDA Expectations During an Inspection

• “…investigators should make every reasonable effort to discuss all observations with management… as they are observed, or on a daily basis to minimize surprises, errors, and misunderstandings when an FDA 483 is issued.”

– IOM 5.2.3
FDA Expectations During an Inspection

• “Industry may use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made…”
  – IOM 5.2.3
FDA activities following the inspection

- Investigators prepare the Establishment Inspection Report (EIR) & recommend classification of the inspection
- Supervisory review
- Classification of inspection: NAI, VAI, OAI
  - If OAI, referral to district’s Compliance Branch for further review & action
483 Observations

- No regulatory requirement to respond to an FDA 483…

…however, it is in your best interests to respond in writing.
Reasons for submitting a well-reasoned, complete, and timely 483 response?
1. Should mitigate an FDA compliance decision to take further action, e.g. untitled letter, Warning Letter
1. “As a general rule, a Warning Letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the letter have been corrected.”

Reasons for 483 response

Demonstrates to the FDA an understanding and acknowledgement of the observations
Reasons for 483 response

Demonstrates to the FDA a commitment to correct, i.e. the intent to voluntarily comply
Reasons for 483 response

Establishes credibility with FDA
Suggestions for addressing 483 observations:
Suggestions for addressing 483 observations:

- **Assess Each Observation**
- **Be specific**
- First, address the specific observation
- Focus on system-wide implications
- **Consider affected products**
You failed to verify that a subset of your finished batches of dietary supplements that you identify through a sound statistical sampling plan, or every finished batch, meet finished product specifications for identity, purity, strength, composition, as required by 21 CFR 111.75(c).
Specifically, during the inspection you stated that you do not perform any finished product testing to verify the identity, purity, strength and composition of your dietary supplement products. Furthermore, your batch records for the following released finished products lacked finished product testing to verify the identity, purity, strength, and composition:
In your response letter dated July 12, 2011, you stated you have hired a second consultant to develop raw material specifications and that you will send raw materials to a contract laboratory for identity testing with a completion time of six months.
We find this response inadequate in that you have not addressed finished product testing or the development of specifications of finished products, as required by 21 CFR 111.70(e).
Case Study on Poor Responses

- Did not address the observation (finished product testing).
- Did not address the specific products cited in the observation.
- What about the raw material and finished product testing for products being produced over the next six months?
Suggestions for addressing 483 observations:

Consider Root-cause Analysis
Focus on the regulatory requirement(s) associated with the observation
Develop action plan to achieve immediate, short-term, and long-term correction and to prevent recurrence
You failed to confirm the identity of other components (not including dietary ingredients) and determine whether other applicable component specifications established in accordance with 21 CFR 111.70(b) are met by either conducting appropriate tests or examinations; or relying on a certificate of analysis (COA) from the supplier of the component that you receive, as required by 21 CFR 111.75(a)(2)
Case Study on Poor Responses

• In order to rely on your suppliers' COAs you must, among other requirements, first qualify the suppliers COAs through confirmation of the results of the supplier's tests or examinations, as required by 21 CFR 111.75(a)(2)(ii)(A).

Specifically, during the inspection it was determined that you do not conduct any testing of raw materials upon receipt.
In your response letter dated July 12, 2011, you stated that your consultant will qualify each of your suppliers per COA with an expected completion time of six months. We find this response to be inadequate in that you do not address the products going to be produced in the next six months prior to your estimated time of completion for the correction.
Suggestions for addressing 483 observations:

Know when to seek outside assistance
Suggestions for Effective Responses

Include a commitment/statement from senior leadership

Address each observation separately
  • Restate the observation and detail how you will address it.

Note whether you agree or disagree with the observation
Suggestions for addressing 483 observations:

Provide corrective action accomplished and/or planned; tell FDA the plan
Be specific (e.g. observation-by-observation)
Be complete
Suggestions for addressing 483 observations:

Be able to deliver what you promise
  • FDA will follow up on your commitments

Address affected products
  • Missing required information

Provide time frames for correction
Suggestions for addressing 483 observations:

Provide method of verification and/or monitoring for corrections
Submit documentation of corrections where reasonable & feasible (err on the side of providing too much documentation)

BE TIMELY!

- Hit your corrective action dates or communicate the delay (and the reason for the delay) to the Agency.
What do the GMPs mean for you?

- Manufacturers will be doing more testing
  - May result in more failures
    - Increased testing cost for suppliers
- Test Methods will become increasingly important
  - Provide these up front to your manufacturers and discuss in detail.
  - Non specific methods such as gravimetric, titrations and UV-vis methods cause difficulty for manufacturers are often difficult to replicate
- Some manufacturers may want to qualify you
  - More requests for documentation
What do the GMPs mean for you?

• Some manufacturers may want to qualify you
  • More requests for documentation
    – This will be one way to separate yourself from your competitors
    – Process flow charts, HACCP plan, information about manufacturing facility
  • Site Audits
    – This means in many instances a greater quality presence
    – Will need to respond to findings with corrective actions
    – Look at putting together a quality manual or site master file; may save you much in the way of resources in the long run and shows commitment to quality
Ingredient Suppliers

FSMA will be important to remember

• Food Safety Modernization Act: signed into law January 4, 2011.
  • Idea is to shift focus of food safety from responding to contamination, to preventing it
  • What does this mean for ingredient suppliers?
FSMA will be important to remember

- FDA Authority under FSMA
  - Mandatory Recall Authority
  - Increased record keeping
  - Bi-annual registration (begin Oct 1, 2012)
    - Must submit new information required added by section 102 of FSMA
      » e-mail address of contact person of facility, or for a foreign facility, email address of the United States agent for the facility, and an assurance that FDA will be permitted to inspect the facility at the times and in the manner permitted by the FD&C Act
FSMA will be important to remember

- FDA Authority under FSMA
  - Increased access to records
    - Foods safety plans and records required documenting implementation
  - FSMA requires certain food testing to be carried out by accredited laboratories
    - directs FDA to establish a program for laboratory accreditation to ensure that U.S. food testing laboratories meet high-quality standards (2 years from enactment)
FSMA will be important to remember

• FDA Authority under FSMA
  • Mandatory preventative controls (Final rule due 18 months after enactment))
    – evaluating the hazards that could affect food safety
    – specifying what preventive steps, or controls, will be put in place to significantly minimize or prevent the hazards
    – specifying how the facility will monitor these controls to ensure they are working
    – maintaining routine records of the monitoring, and (5) specifying what actions the facility will take to correct problems that arise
How will FSAM impact the industry?

• $$$$$$$
  - Suppliers will need to invest to meet the requirements of FSMA leading to higher prices for all foods (ingredients); higher prices at the stores
Thank you!

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