Responding to Data Integrity Issues and Best Practices

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Moderated by John C. (Jack) Garvey, Principal/Chief Executive Officer, Compliance Architects LLC
Responding to Data Integrity Issues:
FDA’s Expectations and Industry Best Practices

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FDA Draft Guidance

- *Data Integrity and Compliance With CGMP: Guidance for Industry* (April 2016)

- Definition of “data integrity”
  
  - *Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)*
Selection of Regulations Cited by FDA Draft Guidance

- Parts 211 and 212
  - § 211.68 (requiring that “backup data are exact and complete,” and “secure from alteration, inadvertent erasures, or loss”)
  - § 212.110(b) (requiring that data be “stored to prevent deterioration or loss”)
  - §§ 211.100 and 211.160 (requiring that certain activities be “documented at the time of performance” and that laboratory controls be “scientifically sound”)
  - § 211.180 (requiring that records be retained as “original records,” “true copies,” or other “accurate reproductions of the original records”)
  - §§ 211.188, 211.194, and 212.60(g) (requiring “complete information,” “complete data derived from all tests,” “complete record of all data,” and “complete records of all tests performed”)

- Part 11
  - Electronic signature and record-keeping requirements
  - Related FDA guidance (*Part 11, Electronic Records; Electronic Signatures — Scope and Application*)
Standard Warning Letter Language for Data Integrity Remediation

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.
B. A current risk assessment of the potential effects of the observed failures on drug quality.
C. A management strategy for the firm that includes the details of a global corrective action and preventive action plan.
Standard Warning Letter Language:
Comprehensive investigation

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility’s operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing, manufacturing and other data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
Standard Warning Letter Language:
Risk assessment

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.
C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company’s data.
- A status report for any of the above activities already underway or completed.
Similarities with FDA’s Application Integrity Policy

▪ In 1991, FDA issued Compliance Policy Guide (CPG) 7150.09, Sec. 120.100, "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities“
  ▪ Often referred to as the “Application Integrity Policy” or “AIP”

▪ **The discovery of [an] extensive pattern of fraudulent data submissions prompted FDA to develop a program:**
  ▪ (1) to ensure validity of data submissions called into question by the agency's discovery of wrongful acts such as fraud, untrue statements of material fact, bribery, and illegal gratuities and
  ▪ (2) to withdraw approval of, or refuse to approve, applications containing fraudulent data.
Example of Similarities with FDA’s AIP: Validity Assessment

<table>
<thead>
<tr>
<th>WL Language</th>
<th>AIP Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>A comprehensive investigation into the extent of the inaccuracies in data records and reporting.</td>
<td>FDA will conduct an investigation to identify all instances of wrongful acts and to determine the extent to which the wrongful acts may have affected approved or pending applications.</td>
</tr>
<tr>
<td>[Applicant will need to conduct] a credible internal review designed to identify all instances of wrongful acts associated with applications submitted to FDA, including any discrepancies between manufacturing conditions identified in approved applications and manufacturing conditions during actual production.</td>
<td></td>
</tr>
</tbody>
</table>
Example of Similarities with FDA’s AIP: Responsible Individuals

<table>
<thead>
<tr>
<th>WL Language</th>
<th>AIP Language</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.</em></td>
<td><em>Identify all individuals who were or may have been associated with or involved in the wrongful acts and ensure that they are removed from any substantive authority on matters under the jurisdiction of FDA.</em></td>
</tr>
</tbody>
</table>
Example of Similarities with FDA’s AIP: Corrective Actions

<table>
<thead>
<tr>
<th>WL Language</th>
<th>AIP Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.</td>
<td>Commit, in writing, to developing and implementing a corrective action operating plan to assure the safety, effectiveness, and quality of their products. . . .The corrective action operating plan will, as appropriate, address procedures and controls to preclude future instances of wrongful acts and noncompliance with regulatory requirements for approved applications, as well as procedures and controls to preclude any recurrences of other violations which may have been found (e.g., a comprehensive ethics program).</td>
</tr>
<tr>
<td>▪ Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.</td>
<td></td>
</tr>
<tr>
<td>▪ Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company’s data.</td>
<td></td>
</tr>
</tbody>
</table>
Questions?
Responding to Data Integrity Issues and Best Practices: A Focus on Good Clinical Practice

Cynthia Schnedar
Executive Vice President, Regulatory Compliance
December 13, 2018
FDLI Enforcement Litigation and Compliance Conference

Greenleaf Health is a full-service regulatory consulting firm guiding companies through the changing FDA landscape.
What is FDA looking for in a GCP Inspection?

- Verify primary efficacy and safety data
- Source of subjects – did subjects exist
- Did subjects meet inclusion/exclusion criteria
- Did IRB conduct review?
- Was informed consent obtained and documented?
- Was protocol followed?
- Was primary efficacy measure verified?
- Were there adverse events?
- What does safety data show? *Eg: EKG*
- Was there accountability – blinding of data?

Common Clinical Investigator Deficiencies*

- Failure to follow the investigational plan/agreement or regulations, or both
- Protocol deviations
- Inadequate recordkeeping
- Inadequate subject protection – informed consent issues, failure to report AEs
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Investigational product represented as safe/effective

*Bioresearching Monitor (BIMO), Fiscal Year 2017 Metrics*
Common S/M/CRO Deficiencies*

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

Bioresearching Monitor (BIMO), Fiscal Year 2017 Metrics
AGENCY’S TOOLKIT FOLLOWING GCP INSPECTIONS

- Form 483
- OAI Classification
- Untitled Letter
- Warning Letter
- Refuse to consider data
- Disqualification/Debarment
- Remove product from market
- Refer for criminal prosecution
ASSESSING DATA INTEGRITY – ALCOA PLUS

Data Integrity

- Attributable
- Legible
- Contemporary
- Original
- Accurate
- Reliable
- Interpretable
- Traceable

Greenleaf Health
CLINICAL INSPECTION SUMMARY

• Prepared by CDER Office of Compliance for CDER Review Division

• Assesses inspections results and may make recommendations, such as:
  • Conduct a sensitivity analysis due to data reliability concerns
  • Conduct additional inspections to verify outstanding issues
  • Consider excluding data generated from all or individual inspected sites
  • Address safety/efficacy concerns
  • Conduct a third-party audit
  • Conduct additional studies
  • Conduct additional analysis
Semler Research Center (SRC), Bangalore, India

- 2015 FDA inspection found documentation indicating subject samples were substituted or manipulated in order for studies to meet the bioequivalence criteria.

- FDA required sponsors who used SRC data for approved or pending products to repeat studies at different firm.

- EMA suspended approved and pending applications relying on SRC data.
DATA INTEGRITY RESOURCES
BEST PRACTICES

• Quality by Design - prepare for an inspection as you design the study
• Keep your records organized and up to date
• Ensure Principal Investigator (PI) is involved and involvement is documented
• Implement Quality Control (QC) and Quality Assurance (QA) procedures
• Ensure compliance with Agency’s guidance on risk based monitoring

SPONSOR’S RESPONSIBILITY

Sponsors Responsible for CROs

• Delegation to CRO for monitoring requires written transfer agreement of obligations - 21 CFR 312.52

• Sponsors retain responsibility for oversight of work completed by CROs

Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
ADEQUATE CONTROLS FOR ELECTRONIC HEALTH RECORDS

- Has it been certified under the Office of the National Coordinator Health IT Certification Program?
- Does it limit access to electronic systems for only authorized users?
- Does it identify authors of records?
- Does it make audit trails available to track changes to data?
- Does it ensure that software updates do not affect the reliability and integrity of the data?
- Does it ensure records are available and retained for FDA inspection for as long as the records are required by applicable regulations?
ACCEPTANCE OF CLINICAL DATA TO SUPPORT MEDICAL DEVICE APPLICATIONS AND SUBMISSIONS, FAQ
BIMO COMPLIANCE PROGRAMS
Homeward Bound: Trends in Data Integrity Issues and How to Hedge Against Supplier DI Issues

December 13, 2018: FDLI Enforcement Conference

A presentation by Douglas Farquhar, Director, Hyman, Phelps & McNamara, P.C. Prepared with the assistance of Charles Snow and Scott Goldman of HPM
Shift in FDA’s enforcement focus

Up until 2012, most Warning Letters for human drug cGMP violations were based on inspections of facilities within the United States.

From 2012 through 2017, a very high percentage of FDA enforcement activity relating to pharmaceutical manufacturing was aimed at non-U.S. facilities.

So far in 2018, we have seen a slight reversal in that trend, with an increasing percentage of drug cGMP Warning Letters originating from domestic inspections, including two for data integrity violations.

- Total CDER cGMP Warning Letters (Worldwide)
- CDER cGMP Warning Letters that Were the Result of a Foreign Inspection

*2018 statistics are current through Nov. 30, 2018
Shift in FDA’s Enforcement Focus?

• Analysis of recent Warning Letters issued by CDER to pharmaceutical manufacturers (excludes compounding pharmacies and WLs for promotional/approval issues) relating to manufacturing issues shows:
  • 30 Warning Letters were issued in 6 months from June 1, 2018 to November 31, 2018.
    • 11 of those letters were issued for facilities in the United States.
      • 2 of the letters alleged violations of data integrity or deficient systems designed to protect data integrity.
  • One trend continues: Many of the cited overseas facilities were subjected to Import Alerts, triggering FDA refusals to permit import into the U.S. of drugs manufactured at those plants and of drugs which use Active Pharmaceutical Ingredients (APIs) from those plants.
## Import Alerts Continue - Drugs

<table>
<thead>
<tr>
<th>Company</th>
<th>Date</th>
<th>Country</th>
<th>Import Alert?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanlim Pharm Co., Ltd.</td>
<td>10/3/2018</td>
<td>South Korea</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Kyowa Hakko Bio Co., Ltd.</td>
<td>8/10/2018</td>
<td>Japan</td>
<td>n/a</td>
</tr>
<tr>
<td>JT Cosmetics &amp; Chemicals Pvt Ltd.</td>
<td>7/27/2018</td>
<td>India</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Les Produits Chimiques B.G.R., Inc.</td>
<td>7/24/2018</td>
<td>Canada</td>
<td>n/a</td>
</tr>
<tr>
<td>Yuki Gosei Kogyo Co., Ltd.</td>
<td>7/17/2018</td>
<td>Japan</td>
<td>n/a</td>
</tr>
<tr>
<td>Claris Injectable Limited</td>
<td>7/5/2018</td>
<td>India</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Zhuhai United Laboratories Co. Ltd.</td>
<td>6/27/2018</td>
<td>China</td>
<td>n/a</td>
</tr>
<tr>
<td>Sichuan Friendly Pharmaceutical Co., Ltd.</td>
<td>6/22/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Henan Lihua Pharmaceutical Co., Ltd.</td>
<td>6/12/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Taiwan Biotech Co., LTD.</td>
<td>5/31/2018</td>
<td>Taiwan</td>
<td>n/a</td>
</tr>
<tr>
<td>IDT Australia Ltd.</td>
<td>5/23/2018</td>
<td>Australia</td>
<td>n/a</td>
</tr>
<tr>
<td>Jilin Shulan Synthetic Pharmaceutical Co., Ltd.</td>
<td>5/14/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Nox Bellcow Cosmetics Co., Ltd.</td>
<td>5/9/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Reine Lifescience</td>
<td>5/9/2018</td>
<td>India</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd.</td>
<td>4/19/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Degasa S.A. De C.V.</td>
<td>4/18/2018</td>
<td>Mexico</td>
<td>n/a</td>
</tr>
<tr>
<td>Keshaya Organics Pvt. Ltd.</td>
<td>3/15/2018</td>
<td>India</td>
<td>n/a</td>
</tr>
<tr>
<td>Labocont Industrial SRL</td>
<td>3/9/2018</td>
<td>Dominican Republic</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Zhejiang Ludao Technology Co., Ltd.</td>
<td>2/23/2018</td>
<td>China</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Alchymars ICM SM Private Limited</td>
<td>2/16/2018</td>
<td>India</td>
<td>n/a</td>
</tr>
<tr>
<td>Cosmecca Korea Co., Ltd.</td>
<td>2/2/2018</td>
<td>South Korea</td>
<td>Import Alert 66-40</td>
</tr>
<tr>
<td>Daito Kasei Kogyo Co Ltd</td>
<td>1/18/2018</td>
<td>Japan</td>
<td>Import Alert 66-40</td>
</tr>
</tbody>
</table>

Of the 50 WLs issued to foreign drug manufacturers for 2018, 22 involved data integrity issues (44%).

Of these 22 WLs concerning data integrity issues, 12 of the companies were also subjected to Import Alert 66-40 (54.5%).

Import Alert 66-40 is “Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs.”
Of the 30 WLs to pharmaceutical companies:
• 11 were issued to facilities in the U.S.
• 7 were based on inspections of facilities in China.
• 4 were based on inspections of facilities in India.
• 3 were issued to facilities in Canada.
• 2 were issued to facilities in Japan.
• 1 was based on an inspection in Europe (France).
• 1 each were issued to facilities in Mexico and South Korea.

Of the 11 WLs which included allegations relating to data integrity:
• 3 were in China.
• 2 were in India.
• 2 were in the U.S (Illinois and Iowa).
• 2 were in Japan.
• 1 was in Canada.
• 1 was in South Korea.
What We Did Wrong:

According to your batch production records, your results were obtained from a “Post Fill Purity Test.” The records are labeled “ANALYTICAL RESULTS OBTAINED BY USING THE (b)(4) OXYGEN ANALYZER.” However, on November 13, 2014, the FDA investigator observed cobwebs between the portable (b)(4) Oxygen Analyzer and the adjacent wall. The general manager stated that your firm does not use the (b)(4) Oxygen Analyzer, which directly contradicts your batch production records.

Further, on November 13, 2014, our investigator reviewed a number of batch records and asked you why all the analytical results reported on these batch production records were identical. Although your batch production records indicate that analytical results were obtained from the (b)(4) Oxygen Analyzer, you responded to the investigator’s question by stating that the values were actually obtained from your supplier’s CoAs. However, the values reported on multiple batch production records disagree with the CoAs for those lots.

We have reviewed your firm’s response in detail. It lacks sufficient corrective actions.
November 6, 2018
WARNING LETTER
Case#: 553686

3. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

You used a texture analyzer to measure in-process gelatin bloom, to test elongation, and to test tensile strength of your (b)(4) patch. Your audit trails on the texture analyzer showed multiple occasions of additional testing that were not reported for your (b)(4) patch, your (b)(4) patch, and your (b)(4) patch. In addition, you performed instances of additional testing that were not reported on a number of products that could not be identified because your electronic data systems were inadequately controlled. Your systems allowed analysts to assign sample names such as “test1” and “test2,” which do not identify or describe analytical samples. You should maintain data throughout all batch record retention periods with all associated metadata required to reconstruct the CGMP activity.
What They Did Wrong:

• Failure to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications/standards
• Investigator observed QC analyst and laboratory team leader signing and backdating a test record.
• Failure to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in records
• Three QC team leaders had administrator privileges within HPLC computerized laboratory software system – they were able to delete/modify files
• Two laboratory software systems had unlocked date/time functions, allowing for manipulation.

October 3, 2018 FDA inspection of Hanlim Pharm Co., Ltd., in South Korea
Not Just Pharmaceutical Companies . . .

Over last three years, Warning Letters to Medical Device companies also show increasing attention to manufacturing plants located in the United States.
• Nearly two-thirds ($\approx 58\%$) of Warning Letters issued were based on inspections at plants in the U.S.
• The percentage of Warning Letters issued to plants in the U.S. has grown over last three years.
Medical Devices and FDA Enforcement

Analysis of Warning Letters issued to medical device manufacturers from July 2011 through November 2018 relating to Quality System (or cGMP) issues shows:
• There were 873 Warning Letters.
• There were 515 Warning Letters (≈ 59%) that related to cGMP issues.
  • Of the 515 cGMP Warning Letters:
    • 345 were the result of a domestic inspection;
    • 170 were the result of a foreign inspection;
    • 81 were the result of an inspection in Asia; and
    • 67 were the result of an inspection in Europe;
    • 13 were the result of an inspection in Canada;
    • 8 were the result of an inspection in South America; and
    • 4 were the result of an inspection in New Zealand or Australia.
Medical Devices and FDA Enforcement

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Device cGMP Warning Letters (Worldwide)</th>
<th>Device cGMP Warning Letters that Were the Result of a Foreign Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>36%</td>
<td>13%</td>
</tr>
<tr>
<td>2014</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>2015</td>
<td>54%</td>
<td>36%</td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*2018 statistics are current through Nov. 30, 2018
## Import Alerts Continue - Devices

<table>
<thead>
<tr>
<th>Company</th>
<th>Date</th>
<th>Country</th>
<th>Import Alert?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boule Medical AB</td>
<td>10/2/2018</td>
<td>Sweden</td>
<td>n/a</td>
</tr>
<tr>
<td>Cardiomed Supplies, Inc.</td>
<td>9/21/2018</td>
<td>Canada</td>
<td>Import Alert 89-04</td>
</tr>
<tr>
<td>Leventon S. A. U.</td>
<td>9/5/2018</td>
<td>Spain</td>
<td>Import Alert 89-04</td>
</tr>
<tr>
<td>Dexcowin Co. Ltd.</td>
<td>2/20/2018</td>
<td>South Korea</td>
<td>Import Alert 89-04</td>
</tr>
</tbody>
</table>

Of the 4 WLs issued to foreign device manufacturers for 2018, 3 of the companies were also subjected to Import Alert 89-04 (75%).

Import Alert 89-04 is “Detention Without Physical Examination of Devices from Firms that Have not met Device Quality System Requirements.”
Medical Device Enforcement

As reported in recent FDA Law Blogpost, FDA notes a 46% increase in medical device inspections in ten years beginning in 2007, and a 243% increase in foreign device inspections

Medical Device Warning Letter

- Your firm does not have any procedures for the monitoring and control of critical process parameters such as: bag vacuum level; grams of (b)(4) delivered; plastic bag serial number; plastic bag size; seal wattage; evaporation temperature; or (b)(4) PSI, during routine sterilization operations.

- Your firm is not monitoring the above process parameters for each sterilization process. During the inspection your firm representatives stated that these sterilization processing records are not maintained as part of your firm’s device history records, and products are released and distributed without review and approval of these parameters.
<table>
<thead>
<tr>
<th>Letter Issue Date</th>
<th>Company Name</th>
<th>Issuing Office</th>
<th>Subject</th>
<th>Close Out Date</th>
<th>US or OUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/6/2018</td>
<td>Reishi D. International, Inc.</td>
<td>San Francisco District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>3/6/2018</td>
<td>Uckele Health &amp; Nutrition, Inc.</td>
<td>Chicago District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
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<tr>
<td>3/9/2018</td>
<td>Carol Bond Health Foods</td>
<td>Dallas District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>3/22/2018</td>
<td>Get The Tea</td>
<td>Denver District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
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<tr>
<td>3/29/2018</td>
<td>Yoder's Good Health Products</td>
<td>Atlanta District Office</td>
<td>Unapproved New Drugs/Dietary Supplements/Adulterated</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>4/30/2018</td>
<td>Chi's Enterprise Inc</td>
<td>Los Angeles District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
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<tr>
<td>5/18/2018</td>
<td>Performance Nutrition Formulators LLC dba VMI Sports</td>
<td>Center for Food Safety and Applied Nutrition</td>
<td>CGMP/Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements/Adulterated</td>
<td>Not Issued *</td>
<td>US</td>
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<tr>
<td>6/6/2018</td>
<td>The Health Management Group Inc.</td>
<td>Cincinnati District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
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<tr>
<td>6/20/2018</td>
<td>KPC Products Inc</td>
<td>Los Angeles District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>7/6/2018</td>
<td>Aegle Nutrition LLC</td>
<td>Dallas District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
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<tr>
<td>7/13/2018</td>
<td>GC Natural</td>
<td>Los Angeles District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>7/16/2018</td>
<td>Lopez Gonzalez Santana Corporation dba Domel and dba Dermixx</td>
<td>San Juan District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US (Puerto Rico)</td>
</tr>
<tr>
<td>8/28/2018</td>
<td>Duy Drugs Inc.</td>
<td>San Juan District Office</td>
<td>Dietary Supplement/New Drug/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>9/7/2018</td>
<td>Best Nutrition Products, Inc</td>
<td>San Francisco District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>10/4/2018</td>
<td>Jinher, Inc.</td>
<td>San Francisco District Office</td>
<td>CGMP/Dietary Supplement/Adulterated/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
<tr>
<td>11/8/2018</td>
<td>Avalon Packaging</td>
<td>Denver District Office</td>
<td>New Drugs/Dietary Supplements/Food Labeling/Misbranded</td>
<td>Not Issued *</td>
<td>US</td>
</tr>
</tbody>
</table>

**Dietary Supplement Manufacturer Warning Letters for 2018**

Current as of December 5, 2018
4. Your batch production record (BPR) did not include complete information relating to the production and control of each batch and did not include all information required in a BPR, as required by 21 CFR 111.255(b) and 21 CFR 111.260. For example, your batch production record for (b)(4) did not include the following:

   a. The identity of equipment and processing lines used in producing the batch [21 CFR 111.260(b)];

   b. The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained [21 CFR 111.260(c)];

   c. The unique identifier that you assigned to each component, packaging, and label used [21 CFR 111.260(d)];

   d. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing [21 CFR 111.260(f)];

   e. The initials of the person responsible for verifying the weight or measure of each component used in the batch [21 CFR 111.260(j)(2)(ii)];

   f. The initials of the person responsible for verifying the addition of components to the batch [21 CFR 111.260(j)(2)(iv)];

   g. Documentation, at the time of performance, of packaging and labeling operations, including the unique identifier that you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels [21 CFR 111.260(k)(1)]. For example, 1,095 labels were issued for (b)(4); however, 1,136 bottles
WARNING LETTER
FY18-HAE6-04

March 6, 2018

VIA UPS

Mr. Michael J. Uckele, CEO
Uckele Health & Nutrition, Inc.
5600 Silverhorn Highway
Blissfield, MI 49228

Dear Mr. Uckele:


3. You failed to prepare a batch record (BPR) every time you manufactured a batch of a dietary supplement as required by 21 CFR 111.255. Specifically, the batch production record for Digestzyme Plus (lots 1940271 and 1995542) failed to contain the following information for a batch record as required in 21 CFR 111.260:

   a. The identity of equipment and processing lines used in producing the batch, as required by 21 CFR 111.260(b).
   b. The date and time of maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross reference to records, such as individual equipment logs, where this information is retained, as required by 21 CFR 111.260(c).
   c. The unique identifier that you assigned to each component, as required by 21 CFR 111.260(d).
   d. The identity and weight or measure of each component used, as required by 21 CFR 111.260(e).
   e. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing, as required by 21 CFR 111.260(f).
   f. The actual results obtained during the monitoring operations, as required by 21 CFR 111.260(g).
   g. The results of any testing or examination performed during the batch production, or a cross-reference to such results, as required by 21 CFR 111.260(h).
   h. Documentation of the manufacture of the batch at the time of performance, as required by 21 CFR 111.260(i), including:

      i. The date on which each step of the MMR was performed, as required by 21 CFR 111.260(j)(1).
      ii. The initials of the persons performing each step, as required by 21 CFR 111.260(j)(2), including:
         § The initials of the person responsible for weighing or measuring each component used in the batch, as required by 21 CFR 111.260(j)(2)(i).
         § The initials of the person responsible for verifying the weight or measure of each component used in the batch, as required by 21 CFR 111.260(j)(2)(ii).
         § The initials of the person responsible for adding the component to the batch, as required by 21 CFR 111.260(j)(2)(iii).
         § The initials of the person responsible for verifying the addition of components to the batch, as required by 21 CFR 111.260(j)(2)(iv).
Trends in FDA Inspection Findings  
(from review of 483s, Warning Letters)

• Data integrity issues and issues with data integrity protections, including:
  • Electronic records systems are not Part 11 compliant.
  • Review of QA and QC data shows duplicate testing, “trial” testing, and “unofficial” testing.
  • Paper test reports and laboratory notebooks are not controlled documents.
  • Failure to include required information and all in-process or finished product test results in batch records
• Additional issues for aseptic processing facilities:
  • Defective smoke studies in aseptic processing areas.
  • Improper investigation of Environmental Monitoring results and Personnel Monitoring results.
• Complaint handling, FDA reporting, investigations
Can You and Your Suppliers Avoid a Bad Inspection?

• Conduct Internal audits
  • Focus on electronic data recording systems
  • Are data backed up routinely at a remote location?
  • Are passwords shared?
  • Are there directories on local drives that contain test results, and, if so, are those test results properly documented?
  • Compare entries on cGMP/QS records with attendance records.
• Encourage unannounced QA visits to ensure that workers are making contemporaneous entries.
• Review manufacturing flow to ensure that reviewers can be present and verify manufacturing steps or tests contemporaneously
Can You and Your Suppliers Avoid a Bad Inspection?

- Mock Inspections:
  - Can find deviations that, if corrected prior to FDA inspection, can mitigate adverse consequences.
  - Can ensure that plant doesn’t bungle arrival of inspectors or handling of inspectors.
  - Ensure inspection SOP is adequate.
- **Diversify supplier network.**
- Do not rely on inspection results from foreign regulators or customers – FDA won’t.