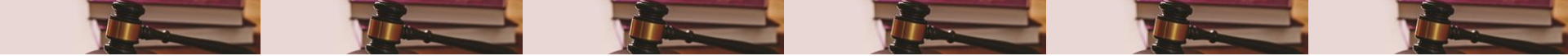

Responding to Data Integrity Issues and Best Practices

Cathy L. Burgess, Partner, Alston & Bird LLP

Douglas B. Farquhar, Director, Hyman, Phelps & McNamara, PC

Cynthia Schnedar, Executive Vice President, Regulatory Compliance, Greenleaf Health, Inc.

Moderated by **John C. (Jack) Garvey**, Principal/Chief Executive Officer, Compliance Architects LLC

FDLI

ALSTON & BIRD

Responding to Data Integrity Issues: FDA's Expectations and Industry Best Practices

Cathy L. Burgess, Esq.
Alston & Bird LLP
Washington, D.C.
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FDA Draft Guidance

- *Data Integrity and Compliance With CGMP: Guidance for Industry* (April 2016)
- Definition of "data integrity"
  - *[D]ata 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Selection of Regulations Cited by FDA Draft Guidance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.

Standard Warning Letter Language: Management strategy

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

WL Language	AIP Language
A comprehensive investigation into the extent of the inaccuracies in data records and reporting.	***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.***
	[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.

Example of Similarities with FDA's AIP: Responsible Individuals

WL Language

Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.

AIP Language

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

Example of Similarities with FDA's AIP: Corrective Actions

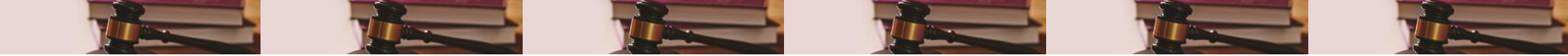
WL Language

- ***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.***
- ***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.***

AIP Language

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).

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

GCP INSPECTIONS

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?

Guidance for Industry: Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. FDA Inspections of Clinical Investigators (June, 2010)

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

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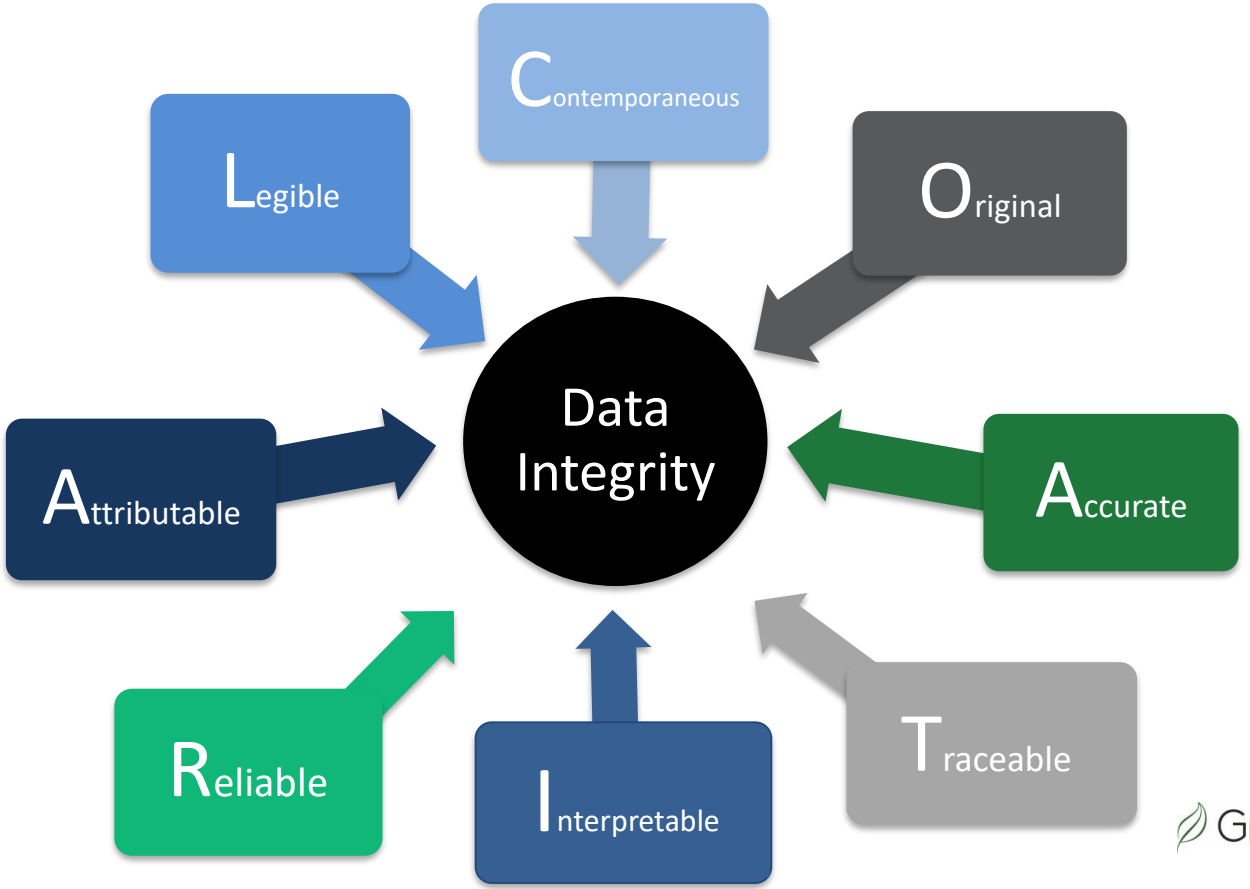
ASSESSING DATA INTEGRITY – ALCOA PLUS



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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

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REJECTED DATA

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

‘Ostracized and criticized’ Indian CRO hits US FDA with $50m lawsuit

By Dan Stanton

29-Jan-2018 - Last updated on 29-Jan-2018 at 12:21 GMT

GettyImages/NiroDesign

RELATED TAGS: United states, Food and drug administration

Semler Research Center says the US FDA caused the “complete annihilation” of its business after regulators rejected bioanalytical studies on the back of data integrity concerns.

in-PharmaTechnologist.com

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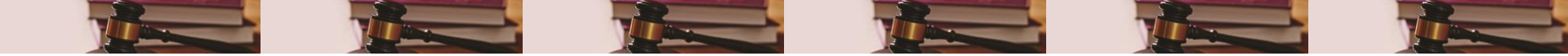

DATA INTEGRITY RESOURCES

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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

Guidance for Industry: *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013).

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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

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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?

Adequate Controls for Electronic Health Records

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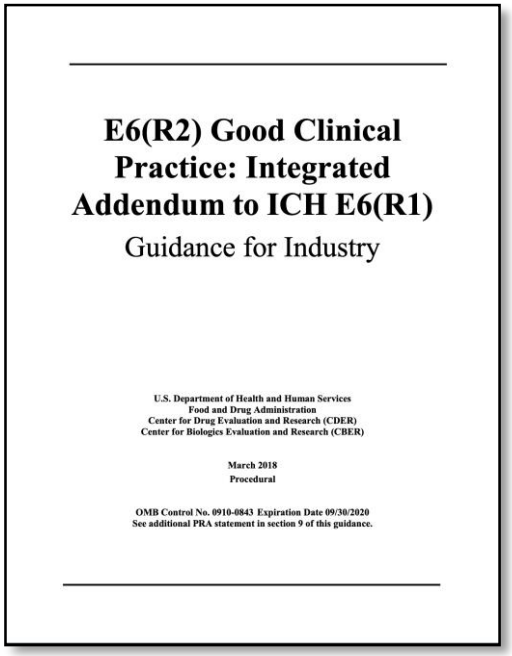
E6(R2) GOOD CLINICAL PRACTICE: INTEGRATED ADDENDUM TO ICH E6(R1)



E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

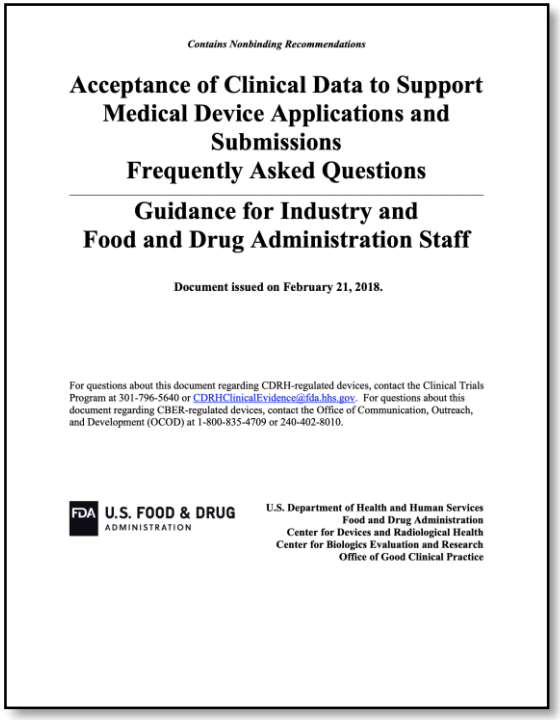
March 2018
Procedural

OMB Control No. 0910-0843 Expiration Date 09/30/2020
See additional PRA statement in section 9 of this guidance.

[E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)]

Greenleaf Health

ACCEPTANCE OF CLINICAL DATA TO SUPPORT MEDICAL DEVICE APPLICATIONS AND SUBMISSIONS, FAQ



Contains Nonbinding Recommendations

Acceptance of Clinical Data to Support Medical Device Applications and Submissions
Frequently Asked Questions

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 21, 2018.

For questions about this document regarding CDRH-regulated devices, contact the Clinical Trials Program at 301-796-5640 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

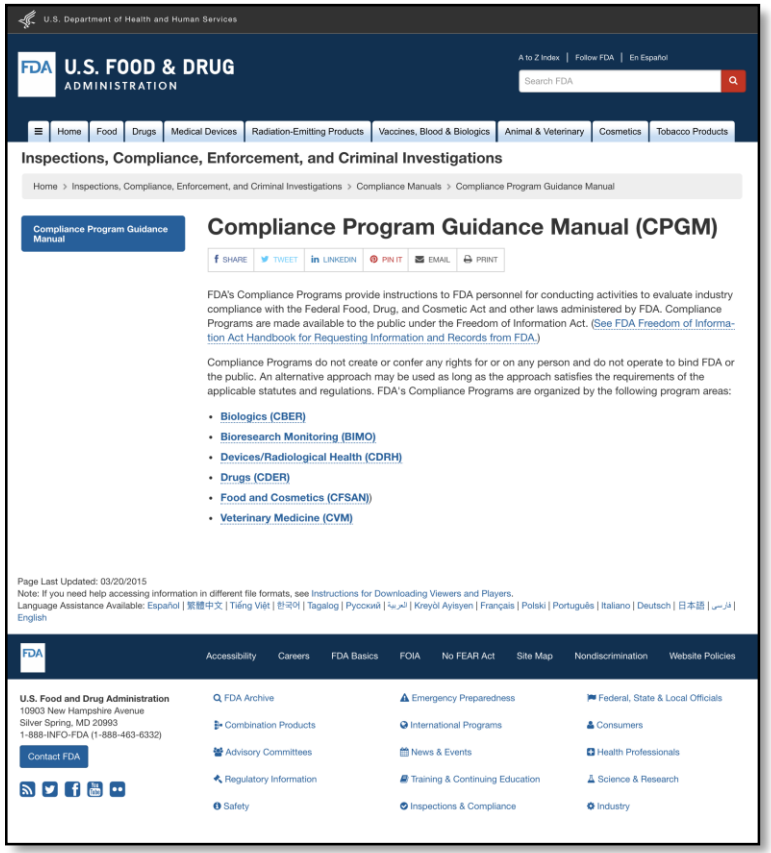
U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Office of Good Clinical Practice

Acceptance of Clinical Data to Support Medical Device Applications and Submissions, Frequently Asked Questions, Guidance for Industry and FDA Staff

Greenleaf Health

BIMO COMPLIANCE PROGRAMS



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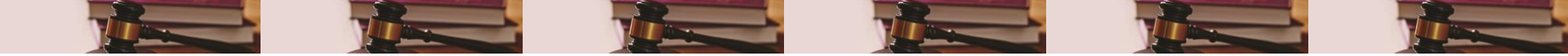
BIMO Compliance Programs



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

FDLI

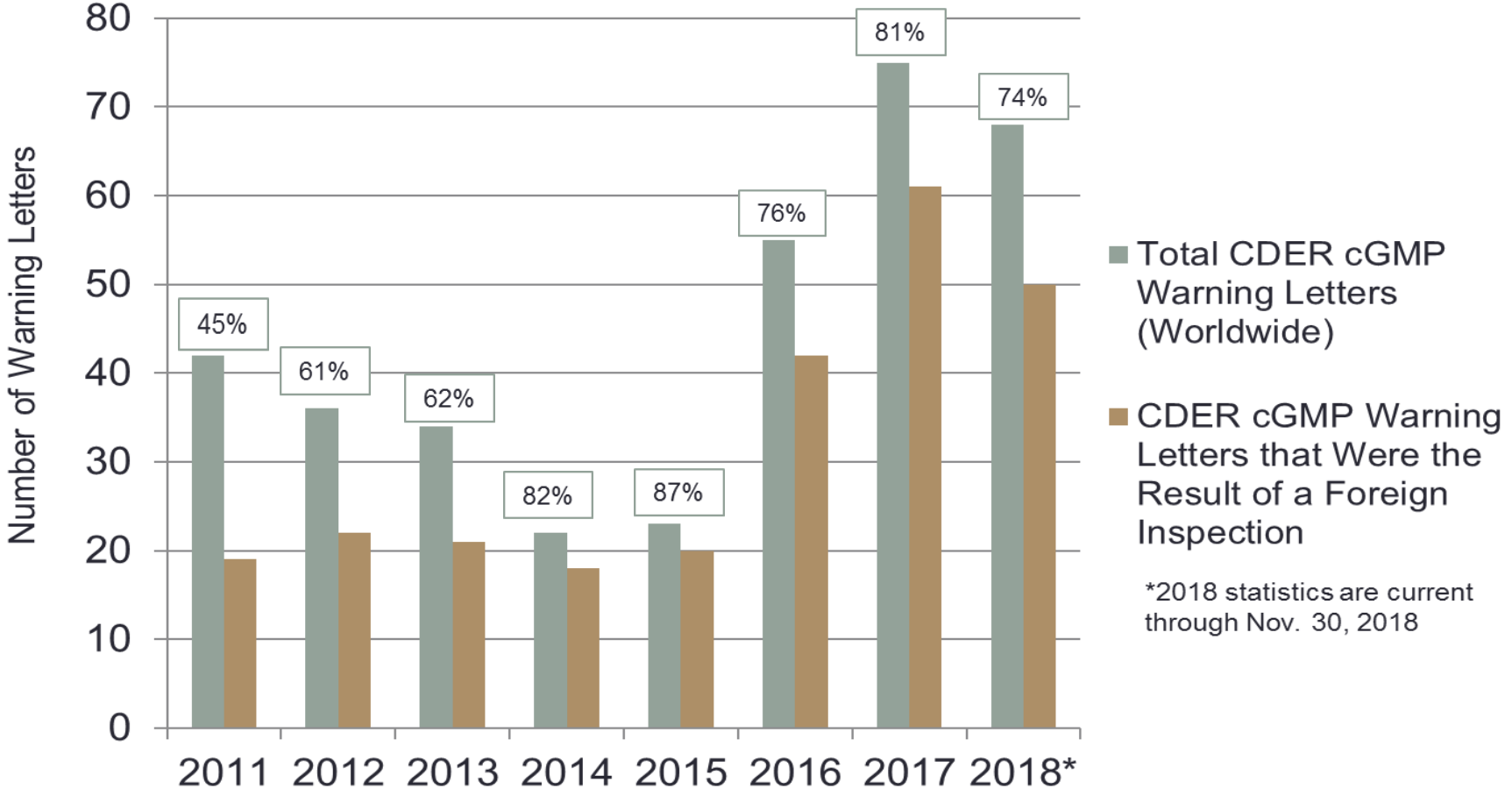
Shift in FDA's enforcement focus

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.

2013-2017 Trend: Higher Percentage of WLs for Foreign Facilities



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

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

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.”

FDA's Enforcement Focus, June through November 2018

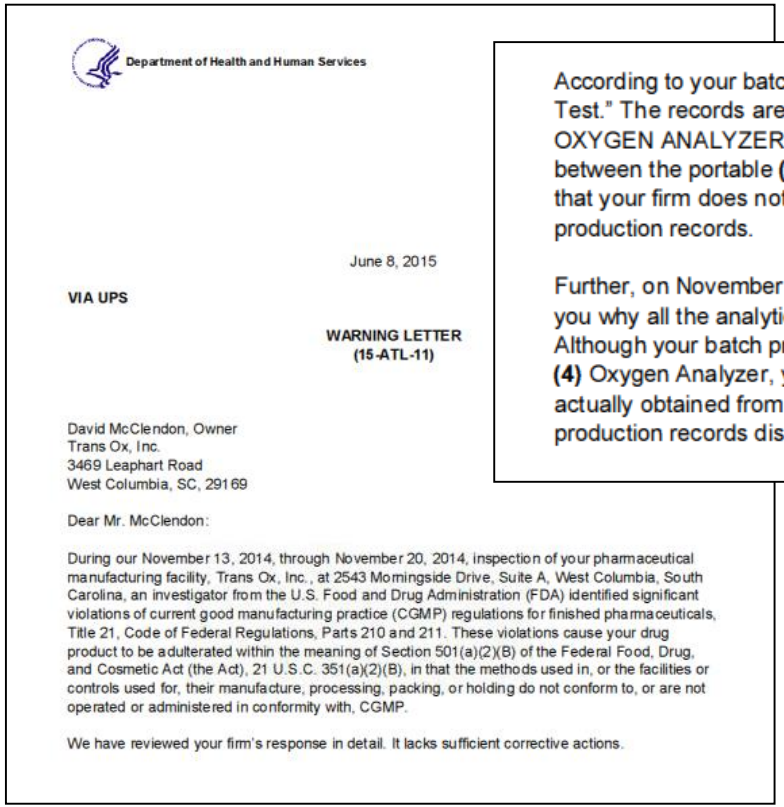
Of the 30 WLs to pharmaceutical companies:

- 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:



Department of Health and Human Services

June 8, 2015

VIA UPS

WARNING LETTER
(15-ATL-11)

David McClendon, Owner
Trans Ox, Inc.
3469 Leaphart Road
West Columbia, SC, 29169

Dear Mr. McClendon:

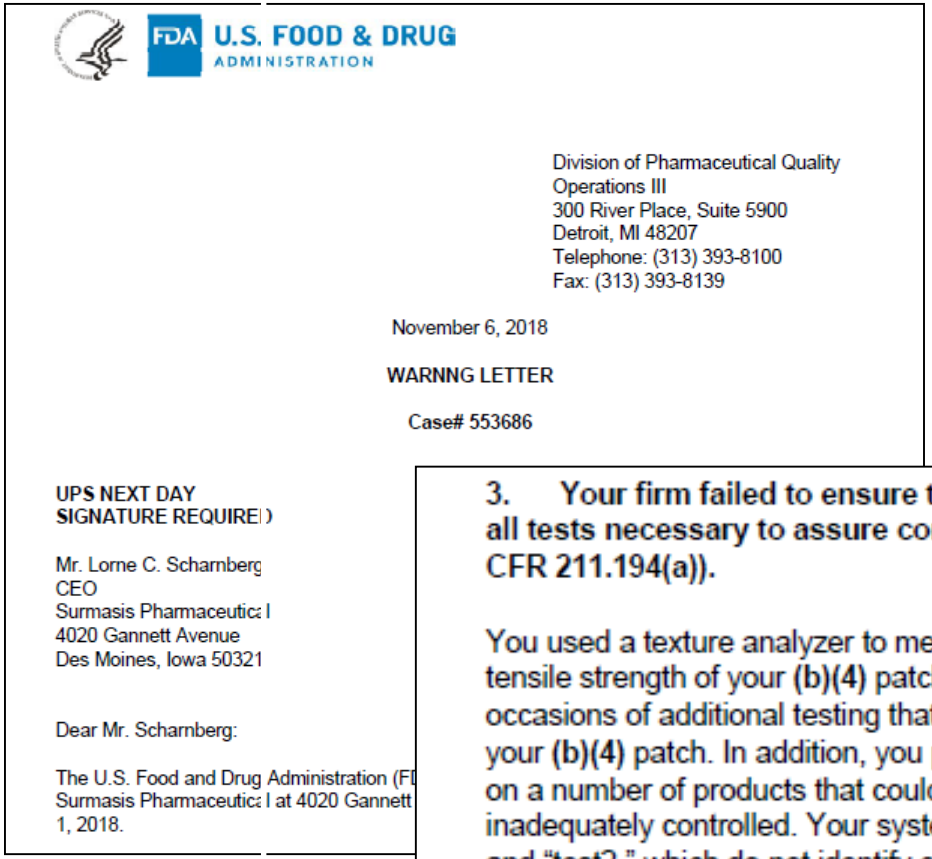
During our November 13, 2014, through November 20, 2014, inspection of your pharmaceutical manufacturing facility, Trans Ox, Inc., at 2543 Morningside Drive, Suite A, West Columbia, South Carolina, an investigator from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response in detail. It lacks sufficient corrective actions.

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.

What We Did Wrong (cont.):



U.S. FOOD & DRUG ADMINISTRATION

Division of Pharmaceutical Quality
Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
Fax: (313) 393-8139

November 6, 2018

WARNNG LETTER

Case# 553686

UPS NEXT DAY
SIGNATURE REQUIRE)

Mr. Lorne C. Scharnberg
CEO
Surmasis Pharmaceutica l
4020 Gannett Avenue
Des Moines, Iowa 50321

Dear Mr. Scharnberg:

The U.S. Food and Drug Administration (FI
Surmasis Pharmaceutica l at 4020 Gannett
1, 2018.

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.

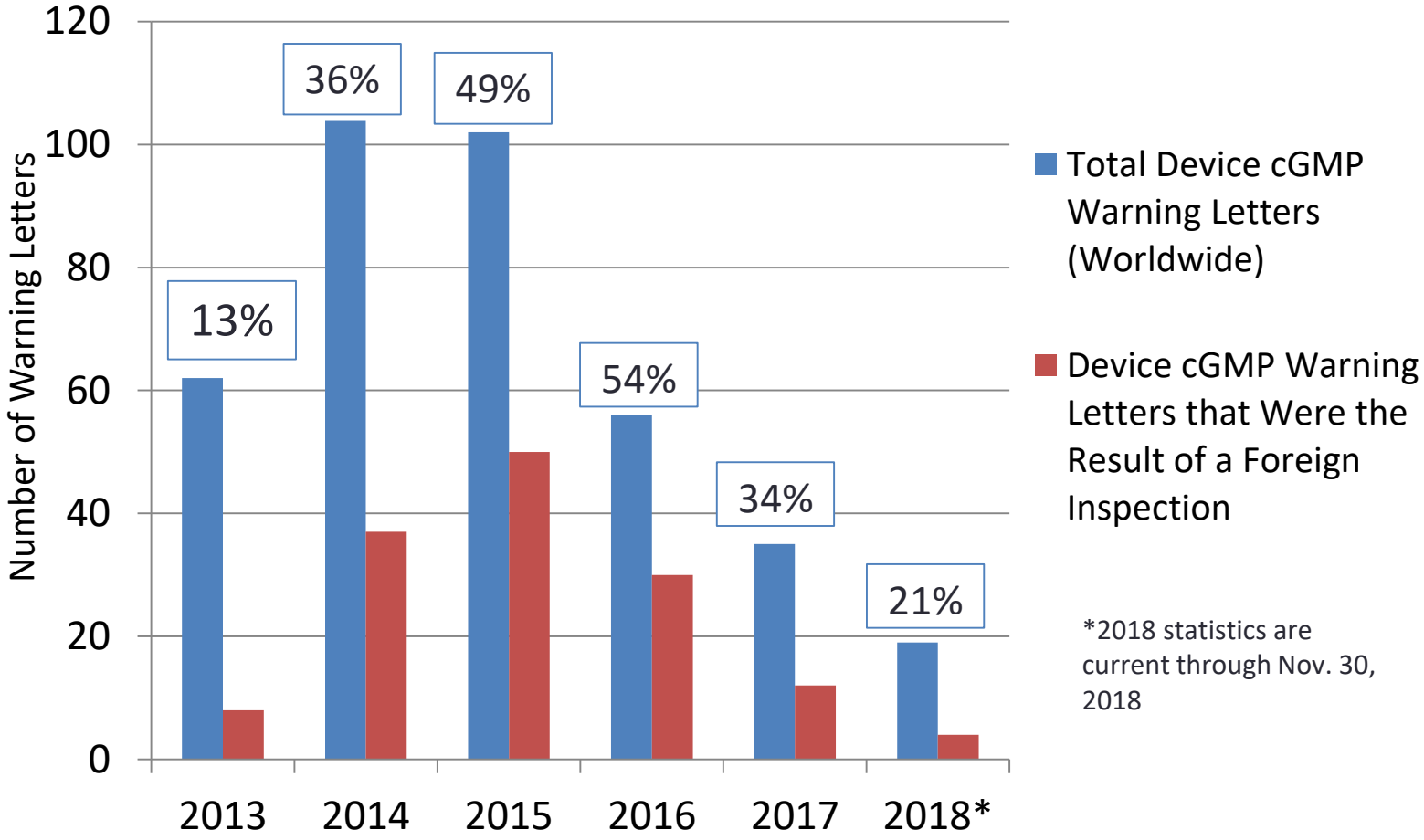
- Nearly two-thirds (≈ 58%) of Warning Letters issued were based on inspections at plants in the U.S.
- The percentage of Warning Letters issued to plants in the U.S. has grown over last three years.

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



*2018 statistics are current through Nov. 30, 2018

Import Alerts Continue - Devices

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

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

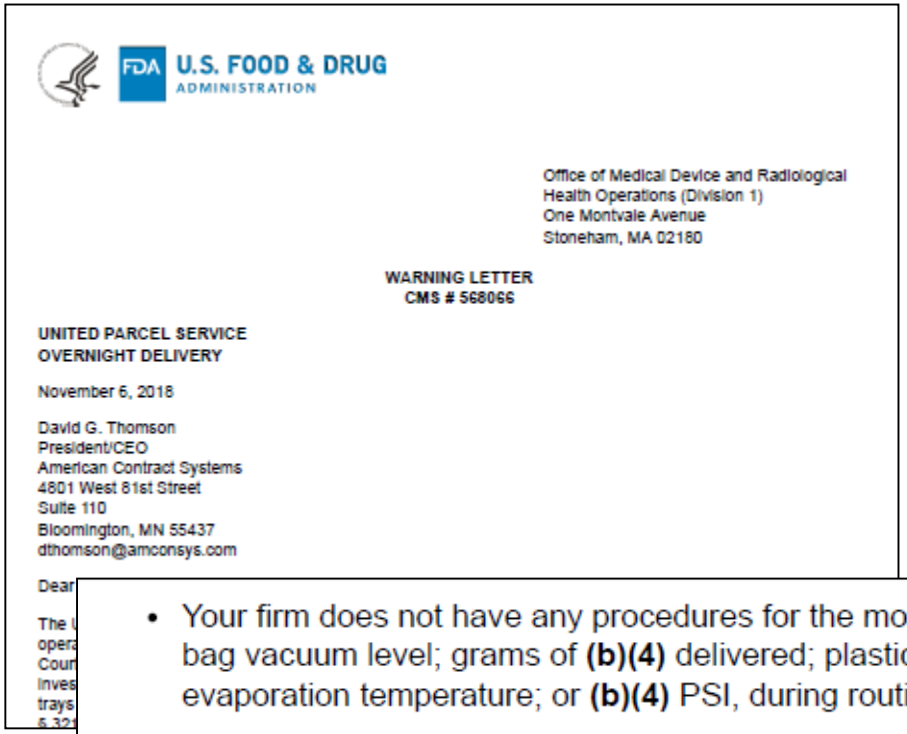
Import Alert 89-04 is “Detention Without Physical Examination of Devices from Firms that Have not met Device Quality System Requirements.”

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 Enforcement and Quality Report,"
posted December 3, 2018, available at www.fdalawblog.net

Medical Device Warning Letter



U.S. FOOD & DRUG ADMINISTRATION

Office of Medical Device and Radiological
Health Operations (Division 1)
One Montvale Avenue
Stoneham, MA 02180

WARNING LETTER
CMS # 568066

UNITED PARCEL SERVICE
OVERNIGHT DELIVERY

November 6, 2018

David G. Thomson
President/CEO
American Contract Systems
4801 West 81st Street
Suite 110
Bloomington, MN 55437
dthomson@amconsys.com

Dear

The
opera
Court
inves
trays

- 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.

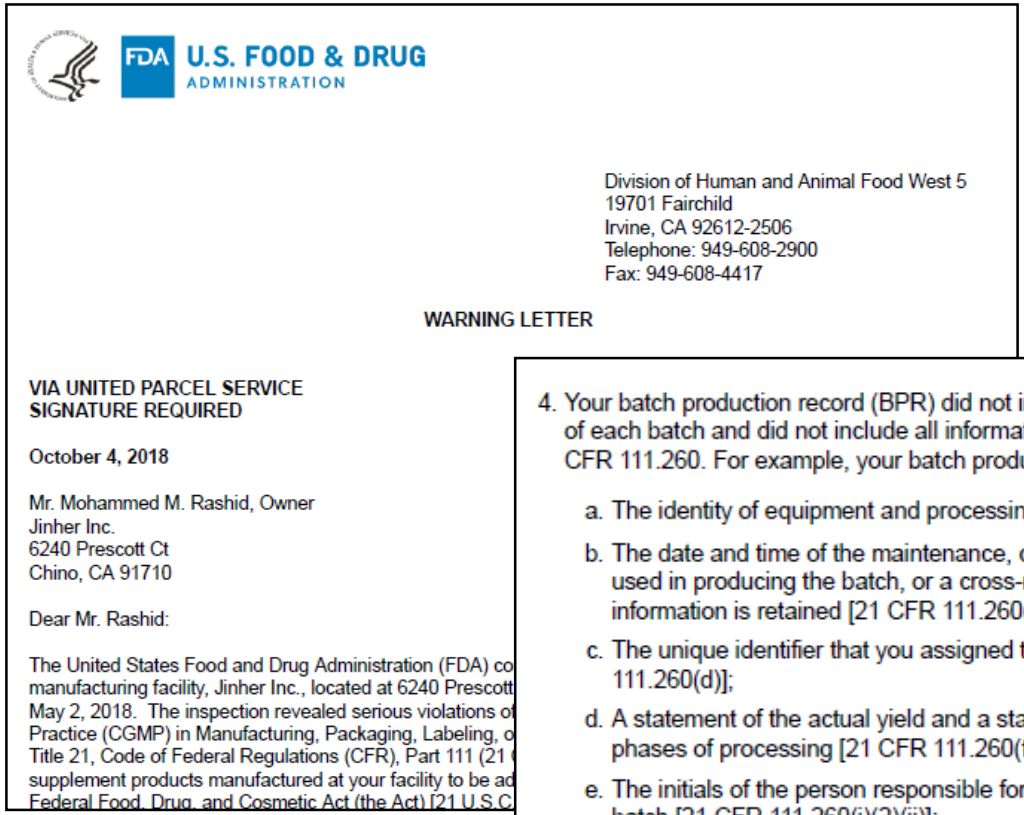
Letter Issue Date	Company Name	Issuing Office	Subject	Close Out Date	US or OUS
2/6/2018	Reishi D. International, Inc.	San Francisco District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
3/6/2018	Uckele Health & Nutrition, Inc.	Chicago District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
3/9/2018	Carol Bond Health Foods	Dallas District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
3/22/2018	Get The Tea	Denver District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
3/29/2018	Yoder's Good Health Products	Atlanta District Office	Unapproved New Drugs/Dietary Supplements/Adulterated	Not Issued *	US
4/30/2018	Chi's Enterprise Inc	Los Angeles District Office	CGMP/Dietary Supplement/Adulterated	Not Issued *	US
5/18/2018	Performance Nutrition Formulators LLC dba VMI Sports	Center for Food Safety and Applied Nutrition	CGMP/Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements/Adulterated	Not Issued *	US
6/6/2018	The Health Management Group Inc.	Cincinnati District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
6/20/2018	KPC Products Inc	Los Angeles District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
7/6/2018	Aegle Nutrition LLC	Dallas District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
7/13/2018	GC Natural	Los Angeles District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
7/16/2018	Lopez Gonzalez Santana Corporation dba Domel and dba Dermixx	San Juan District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US (Puerto Rico)
8/28/2018	Duy Drugs Inc.	San Juan District Office	Dietary Supplement/New Drug/Misbranded	Not Issued *	US
9/7/2018	Best Nutrition Products, Inc.	San Francisco District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
10/4/2018	Jinher, Inc.	San Francisco District Office	CGMP/Dietary Supplement/Adulterated/Misbranded	Not Issued *	US
11/8/2018	Avalon Packaging	Denver District Office	New Drugs/Dietary Supplements/Food Labeling/Misbranded	Not Issued *	US

Dietary Supplement Manufacturer Warning Letters for 2018

Current as of December 5, 2018

Dietary Supplement Manufacturer Warning Letter:

Jinher Inc. (Oct. 4, 2018)



U.S. FOOD & DRUG ADMINISTRATION

Division of Human and Animal Food West 5
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
Fax: 949-608-4417

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

October 4, 2018

Mr. Mohammed M. Rashid, Owner
Jinher Inc.
6240 Prescott Ct
Chino, CA 91710

Dear Mr. Rashid:

The United States Food and Drug Administration (FDA) co
manufacturing facility, Jinher Inc., located at 6240 Prescott
May 2, 2018. The inspection revealed serious violations o
Practice (CGMP) in Manufacturing, Packaging, Labeling, o
Title 21, Code of Federal Regulations (CFR), Part 111 (21
supplement products manufactured at your facility to be ad
Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C.

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

Dietary Supplement Manufacturer Warning Letter:

Uckele Health & Nutrition (Mar. 6, 2018)

U.S. FOOD & DRUG ADMINISTRATION

Chicago District Office
550 W. Jackson Blvd., Suite 1500
Chicago, IL 60661
Telephone: (312) 353-5863
Fax: (312) 596-4187

WARNING LETTER
FY18-HAFE6-04

March 6, 2018

VIA UPS

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

Dear Mr. Uckele:

The United States Food and Drug Administration (FDA) conducted an inspection o
Uckele Health and Nutrition, Inc. located at 5600 Silberhorn Highway, Blissfield, M
September 22, 2017. During the inspection of your firm, FDA identified a number o
Current Good Manufacturing Practices (CGMP) in the Manufacturing, Packaging,
for Dietary Supplement Regulations, under Title 21, Code of Federal Regulations,
111). These CGMP violations cause your dietary supplement products to be adulte
section 402(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C
supplements have been prepared, packed, or held under conditions that do not m
dietary supplements. You may find the Act and its implementing regulations throug
www.fda.gov (http://www.fda.gov/).

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:

- The identity of equipment and processing lines used in producing the batch, as required by 21 CFR 111.260(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).
- The unique identifier that you assigned to each component, as required by 21 CFR 111.260(d).
- The identity and weight or measure of each component used, as required by 21 CFR 111.260(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)
- The actual results obtained during the monitoring operations, as required by 21 CFR 111.260(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).
- Documentation of the manufacture of the batch at the time of performance, as required by 21 CFR 111.260(j), including:
    - The date on which each step of the MMR was performed, as required by 21 CFR 111.260(j)(1).
    - The initials of the persons performing each step, as required by 21 CFR 11.260(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.