Cautionary Tales:
Words to the Wise on Compliance

Vicky C. Stoakes
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To paraphrase…

Those who fail to learn from the mistakes of others are destined to repeat them

~ George Santayana (1863 – 1952)

The "C" in cGMP

FDA regulatory requirements and expectations are continuously evolving

- FDA expects firms to comply with "current" expectations
- Maintaining the status quo can equate to falling behind

"…the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards… It is important to note that CGMPs are minimum requirements."

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm

The "GMP" in cGMP

Some Good Manufacturing Practices (GMPs) have not significantly changed over time…

That being said, the Agency does more fully articulate its expectations based on increased knowledge and experience

A Reality Check

- Each Inspection is a snapshot that typically identifies a limited number of existing deficiencies
  - Beware of developing a false sense of security
  - Inspections should be a supplement to, not substitute for, your own efforts to strenuously challenge the adequacy of your Quality and Compliance Systems on an ongoing basis

"True wisdom is knowing what you don't know"

~ Confucius (551 – 479 BC)

Maintaining cGMP Compliance

Publicly available documents provide insight into FDA regulation, inspectional conduct, and cGMP violations that may warrant enforcement action

- Preambles to FDA proposed and final rules
- FDA Compliance Program Guidance Manuals
  - 7346.832, Pre-Approval Inspections
  - 7356.002, Drug Manufacturing Inspections
  - 7356.002F, Active Pharmaceutical Ingredients
  - 7345.848, Inspection of Biological Drug Products
- Inspection Operations Manual (IOM)
- Compliance Policy Guides
- Regulatory Procedures Manual

Maintaining cGMP Compliance

Additional Resources:

- Judicial Decisions, Consent Decrees, Import Alerts
- Warning Letters, Complete Response Letters, and Untitled Letters
- Inspectional Observations
- Enforcement Reports and Enforcement Activities
- Drug Safety and Availability website
- Recalls, Market Withdrawals, and Safety Alerts website
- Application Summary Reviews
- FDA Email Updates
- FDA Presentations / Webinars
- Conferences, Courses, Industry Publications, Compendial Updates

Maintaining cGMP Compliance

Firms must not only know the cGMP requirements and expectations, but must also appropriately

Disseminate
Evaluate
Apply

these concepts to their own operations as well as those of contractors performing regulated activities

Cautionary Tales

Burkholderia Cepacia Complex

Drugs

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FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products

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[5/22/2017] The FDA advises drug manufacturers of non-sterile, water-based drug products that there have been recent product recalls due to Burkholderia cepacia complex (BCC or B. cepacia) contamination.[1, 2, 3] BCC and other water-borne opportunistic pathogens are among the contaminants that can be found in pharmaceutical water systems.

BCC can survive or multiply in a variety of non-sterile and water-based products because it is resistant to certain preservatives and antimicrobial agents.[4, 5] Detecting BCC bacteria is also a challenge and requires validated testing methods that take into consideration the unique characteristics of different BCC strains.

People exposed to BCC are at an increased risk for illness or infection, especially patients with compromised immune systems.[3, 6]

Specifically, the FDA is reminding drug manufacturers to:

- Establish procedures designed to prevent objectionable microorganism contamination of non-sterile drug products, such as procedures to assure adequate quality of incoming materials, sanitary design, maintenance and cleaning of equipment, production and storage time limitations, and monitoring of environmental conditions (21 CFR 211.113(a)).[7]
- Use scientifically sound and appropriate acceptance criteria (e.g., USP Chapter <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use)[8] and test procedures (e.g., USP <61>/<62> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests and Tests for Specified Microorganisms, respectively) to assure that drug product components (including pharmaceutical water) and finished drug products conform to appropriate quality standards (21 CFR 211.160(b)).

Burkholderia Cepacia Complex

- Provide appropriate drug product specifications (tests, methods, and acceptance criteria) in applications submitted to the FDA (21 CFR 314.50(d)(1) for new drug applications, or 21 CFR 314.94(a)(9) for abbreviated new drug applications). As appropriate, additional laboratory tests may be needed to determine whether products are suitable for release.
- Ensure that the methods used to test finished drug products prior to release for distribution are appropriately validated, accurate, sensitive, specific and reproducible (21 CFR 211.165).
- Test in-process materials during the production process (e.g., at commencement or completion of significant phases, or after storage for long periods), using valid in-process specifications to assure, among other things, that the drug product will meet its final specification, including criteria for absence of microbial contamination, where appropriate (21 CFR 211.110).
- Investigate any failure to meet specifications, including other batches of the same drug product and other drug products that may have been associated with the specific failure or disrepancy(21 CFR 211.192), and implement appropriate corrective and follow-up actions to prevent recurrence.

Adverse events or quality problems experienced with the use of a non-sterile water-based drug product should be reported to FDA's MedWatch Adverse Event Reporting program. Adverse events may be reported in the following ways:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm; or
- Download and complete the form, then submit it via fax at 1-800-FDA-0178.

References:

1. https://www.fda.gov/Drugs/DrugSafety/ucm511527.htm
2. http://www.fda.gov/Safety/Recalls/ucm514358.htm
3. http://www.fda.gov/Safety/Recalls/ucm515610.htm
4. Torbeck L, D. Raccasi, D.E. Guilfoyle, R.L. Friedman, D. Hussong. 2011. Burkholderia cepacia: This Decision is Overdue. PDA J. Pharm. Sci. Tech., 65(5): 535-43. https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM275569.pdf
5. https://www.cdc.gov/mmwr/preview/mmwrhtml/00001358.htm
6. Hutchinson, J., W. Runge, M. Mulvey, G. Norris, M. Yettman, N. Valkova, R. Villemur, and F. Lapine. 2004. Burkholderia cepacia infections associated with intrinsically contaminated ultrasound Gel: The role of microbial degradation of parabens. Infec. Cont. Hosp. Epid., 25: 291-296.
7. As noted in the preamble to the 1978 CGMP final rule, parts 210/211, "Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them. A definition of the term is not practical in the regulations, however, because the objectionable nature of a microorganism may develop only in relation to the unique circumstances of a particular formulation, a particular ingredient, a particular method of manufacture, or the conditions found at a particular firm." 43 FR 45053.
8. Guidance for Industry: Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073423.pdf

Burkholderia Cepacia Complex

7. As noted in the preamble to the 1978 CGMP final rule, parts 210/211, "Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them. A definition of the term is not practical in the regulations, however, because the objectionable nature of a microorganism may develop only in relation to the unique circumstances of a particular formulation, a particular ingredient, a particular method of manufacture, or the conditions found at a particular firm." 43 FR 45053.

Burkholderia Cepacia Complex

FDA Warning Letter

"Your drugs are often used in hospital or clinical settings in which patients may have a higher vulnerability to infection with *B. cepacia* and other objectionable organisms. Detecting numbers and types of objectionable microorganisms in your products is critical to making appropriate batch disposition decisions, yet the microbiological screening method on which you rely to examine your products for the presence of microbiological contamination has not consistently and reliably detected the presence of *B. cepacia* in your drugs before you released them for distribution. For example, since 2006, your firm conducted at least four recalls for products associated with *B. cepacia* contamination, including…

Burkholderia Cepacia Complex

FDA Warning Letter, continued

"…Had your firm been utilizing a screening method capable of consistently detecting *B. cepacia*, these products may not have been released in the first instance."

"Your acceptance criteria …failed to include *B. cepacia* on the list of objectionable organisms. This is despite the fact that your facility has a history of recurring *B. cepacia* contamination issues and that a 2016 root cause investigation conducted in your facility revealed a biofilm had become established within the Clean-in-Place (CIP) system ... Your firm cultured and identified *B. cepacia* within these cleaning samples from the CIP system."

Burkholderia Cepacia Complex

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Safety Alerts for Human Medical Products

2017 Safety Alerts for Human Medical Products

2016 Safety Alerts for Human Medical Products

Liquid Drug Products Manufactured by [redacted] and Distributed by [redacted] and Possibly Other Companies: FDA Advisory - Not to Use

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[Posted 08/08/2017]

AUDIENCE: Pharmacy, Patient, Health Professional

ISSUE: FDA is advising health care professionals and patients not to use any liquid product manufactured by [redacted] due to Burkholderia cepacia contamination and the potential for severe patient infection [redacted] announced a voluntary recall on August 3, 2017, of two such products – Diocto Liquid and Diocto Syrup, both oral liquid docusate products – manufactured by [redacted].

Additional liquid drug products manufactured by [redacted], might also be affected. Such products might have been labeled and distributed by [redacted] and other companies. Any company that purchased liquid products manufactured by [redacted], should immediately quarantine material under their control and contact the local FDA pharmaceutical recall coordinator.

Centers for Disease Control and Prevention laboratory testing of [redacted]'s oral liquid docusate detected a strain of B. cepacia, bacteria linked to recent patient infections. Therefore, FDA recommends health care professionals and patients not use [redacted]'s liquid drug products.

BACKGROUND: In 2016, FDA advised health care professionals and patients not to use liquid docusate drug products manufactured at [redacted], facility after being implicated in CDC's public health investigation. These products were labeled and distributed by multiple companies, including [redacted]. An FDA

Burkholderia Cepacia Complex

FDA advises health care professionals and patients not to use any liquid drug products manufactured by [redacted] and distributed by [redacted] and possibly other companies

CDC lab testing detects product contamination, links products to patient infections

[8/8/2017] FDA is advising health care professionals and patients not to use any liquid product manufactured by [redacted] due to *Burkholderia cepacia* contamination and the potential for severe patient infection.

[redacted], announced a voluntary recall on August 3, 2017, of two such products – Diocto Liquid and Diocto Syrup, both oral liquid docusate products – manufactured by [redacted]

Additional liquid drug products manufactured by [redacted] might also be affected. Such products might have been labeled and distributed by [redacted] and other companies. Any company that purchased liquid products manufactured by [redacted] should immediately quarantine material under their control and contact the local FDA pharmaceutical recall coordinator.

Centers for Disease Control and Prevention laboratory testing of [redacted]'s oral liquid docusate detected a strain of *B. cepacia*, bacteria linked to recent patient infections. Therefore, FDA recommends health care professionals and patients not use [redacted]s liquid drug products.

Patients, pharmacies, and health care facilities should immediately stop using and dispensing all liquid products manufactured by [redacted]. It might be difficult to determine the manufacturer because these liquid products are not labeled with a [redacted] label. FDA advises health care facilities and pharmacies that think they might have liquid [redacted] drug products, especially oral liquid docusate drug products, to check with their supplier to determine the identity of the manufacturer.

Patients who are using liquid drug products and who have concerns should contact their health care professional.

In 2016, FDA advised health care professionals and patients not to use liquid docusate drug products manufactured at [redacted], facility after being implicated in CDC's public health investigation. These products were labeled and distributed by multiple companies, including [redacted] An FDA investigation associated with a 2016 multistate outbreak identified *B. cepacia* in more than 10 lots of oral liquid docusate sodium manufactured by [redacted], which was linked to patient infections that required intensive medical treatment. The 2016 investigation also detected *B. cepacia* in the water system used to manufacture the product.

FDA reminds manufacturers of the importance of robust manufacturing and testing of liquid products to ensure low levels of microorganisms and the absence of any that might cause infection.

Burkholderia Cepacia Complex

- Consider whether sufficient microbiology expertise exists to assure microbial control of manufactured APIs and drug products
- Ensure personnel receive microbiological training necessary to execute regulatory responsibilities
- Evaluate whether appropriate bioburden control program has been established and implemented
- Assess if proper system has been established for recovery and identification of organisms and determination whether such are objectionable

Data Integrity

CP 7346.832, Pre-Approval Inspections

Provides possible indications of data integrity problems, including:

- Alteration of raw, original data and records
- References to failing bio-studies
- Discrepancies (e.g., color, shape, embossing) between biostudy samples and reserve samples
- Inconsistencies in manufacturing documentation (e.g., identification of actual equipment used) and other information in the submission

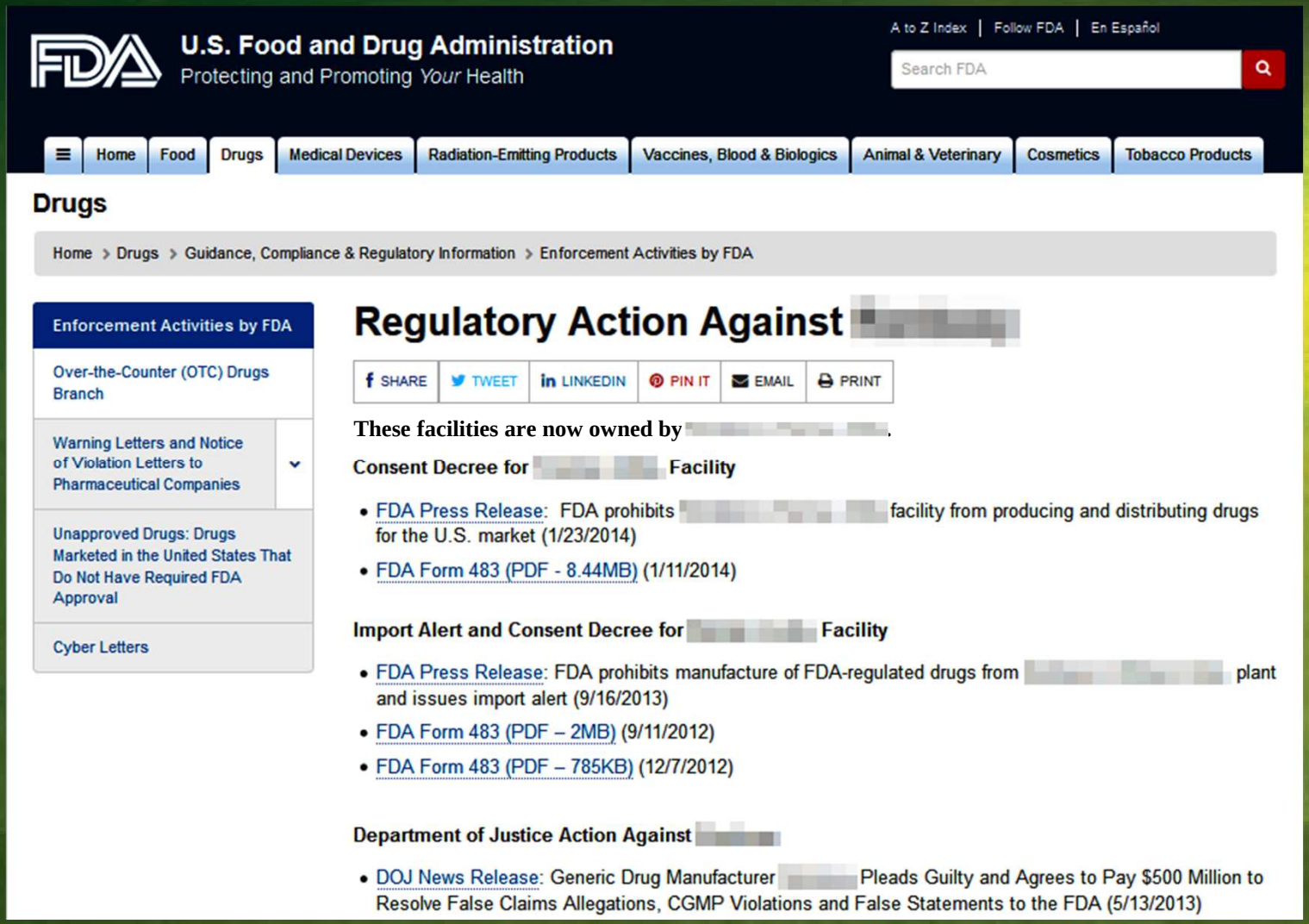
Data Integrity

CP 7346.832, Pre-Approval Inspections

Provides examples of data integrity problems that have been previously observed, including:

- Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
- Creating acceptable test results without performing the test
- Backdating stability test results to meet the required commitments
- Reworking or process modifications not adequately justified and appropriately reported
- Determination that a site does not actually manufacture the drug as described in records or submissions

Data Integrity



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Regulatory Action Against [redacted]

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These facilities are now owned by [redacted].

Consent Decree for [redacted] Facility

- FDA Press Release: FDA prohibits [redacted] facility from producing and distributing drugs for the U.S. market (1/23/2014)
- FDA Form 483 (PDF - 8.44MB) (1/11/2014)

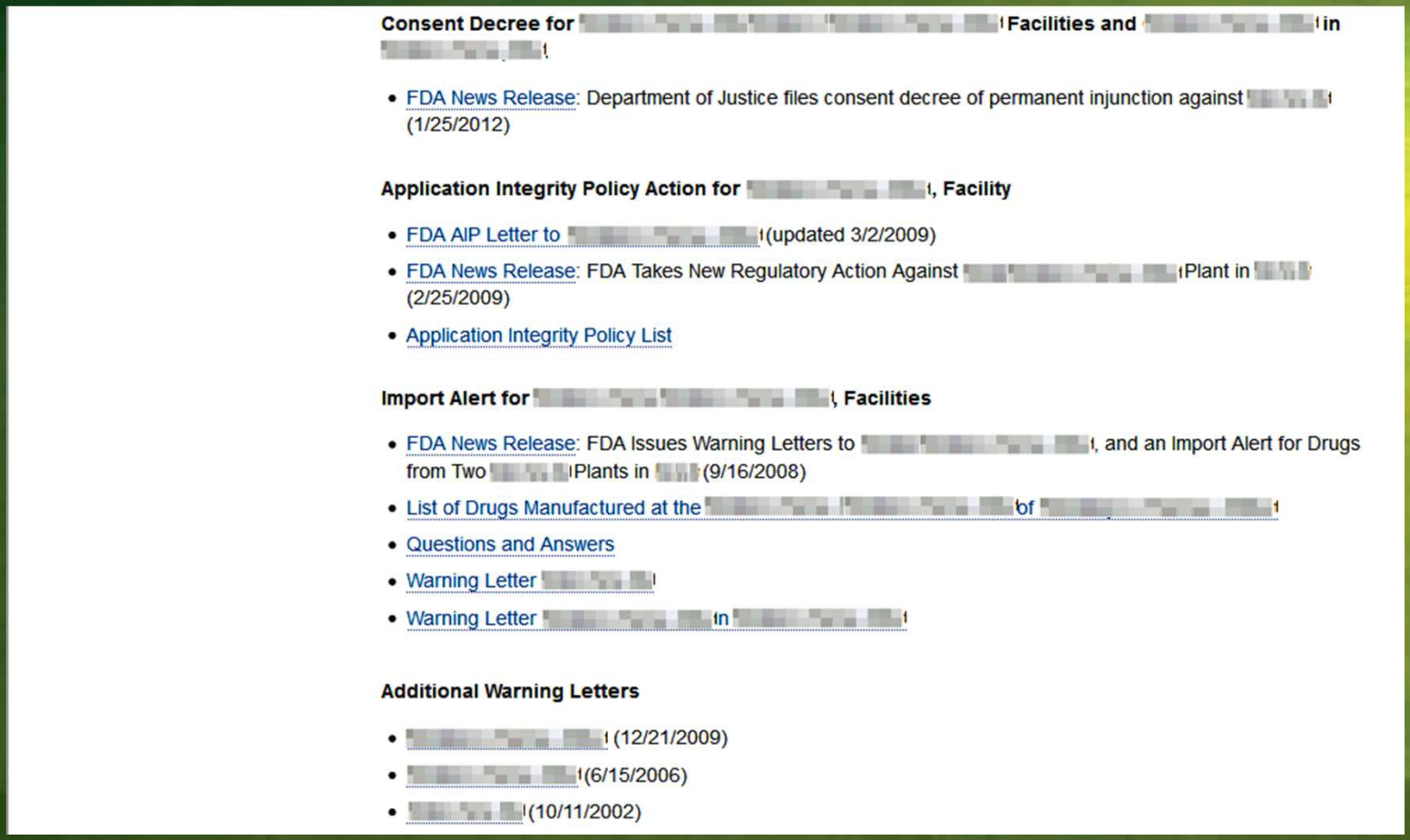
Import Alert and Consent Decree for [redacted] Facility

- FDA Press Release: FDA prohibits manufacture of FDA-regulated drugs from [redacted] plant and issues import alert (9/16/2013)
- FDA Form 483 (PDF – 2MB) (9/11/2012)
- FDA Form 483 (PDF – 785KB) (12/7/2012)

Department of Justice Action Against [redacted]

- DOJ News Release: Generic Drug Manufacturer [redacted] Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, CGMP Violations and False Statements to the FDA (5/13/2013)

Data Integrity



Consent Decree for [redacted] Facilities and [redacted] in [redacted]

- FDA News Release: Department of Justice files consent decree of permanent injunction against [redacted] (1/25/2012)

Application Integrity Policy Action for [redacted], Facility

- FDA AIP Letter to [redacted] (updated 3/2/2009)
- FDA News Release: FDA Takes New Regulatory Action Against [redacted] Plant in [redacted] (2/25/2009)
- Application Integrity Policy List

Import Alert for [redacted], Facilities

- FDA News Release: FDA Issues Warning Letters to [redacted], and an Import Alert for Drugs from Two [redacted] Plants in [redacted] (9/16/2008)
- List of Drugs Manufactured at the [redacted] of [redacted]
- Questions and Answers
- Warning Letter [redacted]
- Warning Letter [redacted] in [redacted]

Additional Warning Letters

- [redacted] (12/21/2009)
- [redacted] (6/15/2006)
- [redacted] (10/11/2002)

Data Integrity

FDA Warning Letter

> "Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data. Your HPLC computer software lacked active audit trail functions to record changes to analytical methods... In addition, your laboratory systems did not have access controls to prevent deletion or alteration of raw data…"
>
> "…Moreover, the gas chromatograph (GC) computer software lacked password protection allowing uncontrolled full access to all employees. "

Data Integrity

FDA Warning Letter, continued

"... However, your response lacks sufficient detail of the systems and controls you will implement. Simply turning on audit trail functions is inadequate… "

"…provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computerized systems during the manufacture and testing of your drugs. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacturing and testing that generates electronic raw data. Your response should also describe the controls and procedures you will implement to retain and archive the raw data you generate. "

Data Integrity

- Determine if organizational functions and contractors performing regulated activities have adequate systems, knowledge, and resources to ensure data integrity as pertain to their area(s) of responsibility
  - Auditing is only one component of a systematic approach
  - Build integrity into the process via: Corporate culture; Quality systems and procedures; Computer System Validation and 21 CFR Part 11 compliance; Training; Oversight and monitoring; etc.
- Conduct thorough Gap Assessment and develop documented remediation plan
- Solicit advice: legal, third party consultants, software vendors
- Take a global, holistic approach to remediation efforts

Facility Compliance Status

FDA CDER Summary Review

Prior to NDA submission, FDA inspections revealed cGMP violations at the drug substance and product manufacturing site. After NDA submission, a Warning Letter was issued. FDA could not establish that drug substances and finished products were no longer deemed adulterated before the PDUFA goal date. Compliance made a withhold approval recommendation and the application received a complete response due to product quality issues.

Facility Compliance Status

Complete Response Letter

Pharmaceutical company announced that FDA issued a Complete Response Letter to its NDA. The company had received a final approval for the product. However, FDA rescinded its earlier approval, citing that the compliance status of the manufacturing facility was not acceptable on the date of approval.

Facility Compliance Status

FDA Warning Letter

"Our investigators found that you sourced material from a facility on FDA Import Alert 66-40 for failure to meet CGMP requirements. Specifically, you obtained and used material for the manufacture of **(b)(4)**, an API intermediate for the **(b)(4)** drug **(b)(4)**, from **(b)(4)** facility at **(b)(4)**. The **(b)(4)** facility has been on FDA Import Alert 66-40 since **(b)(4)**, and was issued Warning Letter **(b)(4)** stating that **(b)(4)** API are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act. In addition, you used the **(b)(4)** site to store and test stability samples."

Facility Compliance Status

FDA Warning Letter, continued

"Your response is inadequate. You did not perform a sufficient risk assessment for use and release of drugs manufactured using in-process material from **(b)(4)** facility.

In response to this letter, provide the following:

- an action plan to ensure the quality of your drugs, i.e., by notifying customers about adulterated material in your drug manufacturing process and recalling any adulterated drugs for U.S. distribution still within expiry;
- stability testing and analysis from an independent laboratory for all lots of drugs within expiry for U.S. distribution;
- a summary report of any corrective actions that you have implemented or plan to implement based on your consultant's review of stability studies. "

Facility Compliance Status

- Rigorously evaluate and monitor the compliance status of facilities before and throughout the submission process and during commercialization
- Recognize significant cGMP observations and assess the potential impact from a compliance perspective
- Know when to involve legal counsel and/or independent experts
- Be cognizant of significant potential compliance risks, develop appropriate remediation strategies, and consider developing contingency plans

Accountability

FDA Warning Letter

> "Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), you are ultimately responsible for the quality of your products. Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the Act and its implementing regulations…"

Accountability

FDA Warning Letter

> "FDA considers contractors as extensions of the manufacturer's own facility. Your failure to comply with CGMP may affect the quality, safety, and efficacy of the products you test for your clients. Your clients (e.g., drug manufacturers, application sponsors), in turn, must provide you with all of the scientific data and information needed to support reliable method implementation"

Accountability

The Supreme Court addressed the duty imposed on responsible corporate officials in the case of United States v. Park (1975):

- "The [FDCA] imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur."

- "The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding, and perhaps onerous, but they are no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public that supports them."

- The Court did not impose on the Government a duty to prove that the defendant had a consciousness of wrongdoing.

Accountability

- Examine systems and procedures to assure critical compliance issues are escalated to the attention of Executive management
- Evaluate whether Quality has necessary authority and resources and exercises them appropriately
- Determine if employee staffing, experience, and training are adequate to meet regulatory obligations
- Assure responsibility for quality belongs to every employee
- Assure personnel ratings / rewards consistently encourage quality and compliance minded performance
- Assess the adequacy of contractual provisions pertaining to regulated activities and Quality Agreements

"Accountability breeds response-ability."

Stephen R. Covey (1932 – 2012)

Final Thoughts…

Consider whether your firm and contractors routinely operate in firefighting mode

If so, this may negatively impact the ability to stay current in a complex and continuously evolving regulatory environment

Final Thoughts…

To ensure long-term regulatory compliance, it is essential to:

- Purposefully monitor current application of GMP regulations
- Critically evaluate knowledge acquired to identify potential risks
- Strenuously challenge the adequacy of existing Quality and Compliance Systems
- Communicate findings to Senior Management

Final Thoughts…

- When current expectations are met or exceeded:

Take Credit!!!

(Without developing a false sense of security or becoming complacent)

- When current expectations are not met:
  - Prepare a documented remediation strategy, including timelines for completion and assignment of responsibilities
  - Request and justify resources to achieve timely, effective, and sustainable remediation