INDUSTRY PERSPECTIVES ON THE CHANGES IN REGULATORY AND ENFORCEMENT ACTIVITIES
It takes energy to maintain any system in a complex ordered state
CMC Quality

Product & Process Development
Risk Mgmt
Product Transfers
CAPA
Knowledge Mgmt
Analytical Services
CMC Governance
Keeping up with ever-increasing volume and constantly-raising expectations
Ever Increasing Expectations: Supplier Quality is Experiencing Lifecycle Scrutiny

Sharp increase in negative trends in BOTH ends of the lifecycle requires an end-to-end approach for Supplier Quality Management

Pre-Approval Phase
Supplier issues preventing Drug Mfg. approvals (CRLs)

Commercial Phase
Supplier issues Creating drug shortages, recalls, and import alerts

- Demo and Validation
- Alternative Suppliers
- Supplier Selection
- Monitoring and Improving

Product Realization
Regulatory Scrutiny of Third-Party Suppliers and Manufacturers
Filing Impact

Europe delays Merck & Co.'s HCV drug on back of CMO quality issues

Inadequate record keeping at Merck & Co.'s contract manufacturer has delayed the European launch of its hepatitis C drug Zepatier (elbasvir and grazoprevir). Read...

Bend Research Inc SONC. Now being inspected by FDA

Biotech

UPDATED: AstraZeneca’s $2.7B hyperkalemia drug ZS-9 rejected by FDA

“The CRL refers to observations arising from a pre-approval manufacturing inspection,” [Corden Pharma (Italy) WL]

FiercePharmaManufacturing - | 05.26.16 | Pfizer manufacturing delay creates problems for syphilis patients; EMA inspectors savage Dhanuka Labs Indian plant

Dhanuka Laboratories (India) SONC

Catalent softgel plant hit with US FDA 483 while client Opko receives CRL

CRL issued in a matter of days

MINSHENG GROUP SHAOXING PHARMACEUTICAL CO. LTD, China

Overall, 18 deficiencies were observed during the inspection, including 2 Critical Falsification of source of API (Thiamphenicol): Repackaging, relabeling and company/Zhejiang Runkang Pharmaceutical Sonc – Falsification of API
EU Full Year 2016 Industry Review
Statements of Non-Compliance (SONC)

- Active Pharmaceutical Ingredient (API) sites: 39%
- Non-Sterile Product Sites: 31%
- Sterile Product Sites: 30%

EU has cited:
- Data Integrity
- Quality Mgmt.
- Production Controls
- Supply Chain Controls
- Lack of Sterility Assurance
- Batch Cert.
- Validation
- Facilities
- Contamination
- Falsification of Documentation

SONC by Causes

SONC by Country
FDA Complete Response Letters (2010-current)*

Dramatic decrease in NDA Approvals in 2016
- Drop of Nearly 50% in total number of NME:
- Increased number CRLs
  - Globalization of manufacturing (i.e., more facilities) and more complex manufacturing
  - More complex products
  - ~85% of CRLs cited issues with quality
  - Between 2010 through 2015 only 9% cited cGMP issues as the primary deficiency

*No data from 2012
FDA Data Integrity Findings Continue at Indian Firms, Highlighting Challenges in Changing a Facility’s Quality Culture

FDA investigators are continuing to uncover serious data integrity issues at facilities in India, in a story highlighting the challenges regulators face in getting companies to make changes in their quality culture and interactions with FDA investigators.

Since the middle of 2013, seven Indian firms have received warning letters referencing the integrity of their manufacturing practices and interactions with FDA investigators.

Data Integrity Concerns at Italian API Manufacturer

FDA aggressively looking for data integrity problems in inspections

2016 Drug GMP Warning Letters By Facility Type

FDA GMP Warning Letters Review: Rate Soared In 2016 On Sterility And Data Integrity Concerns
• “Of 26 warning letters to API firms, 16 focused on data integrity issues, including eight to sites in China and five to sites in India.”

• “Of 30 warning letters to drug product facilities, 18 went to OTC firms, most of them abroad, for failure to accomplish basic GMP functions. Many of these firms were focused on cosmetics and hygiene products. Some did not appear to realize they were also manufacturing what FDA considers drug products, or to understand what that entails.”

• “4 warning letters went to “multi-product” facilities that manufacture both APIs and drug products.”

• “Of 56 warning letters to pharmacies, 21 went to facilities that had registered as outsourcing pharmacies. The rest asserted they were operating as traditional compounding pharmacies, but FDA found on inspection that many did not qualify. All but two of the pharmacy warning letters focused on sterility assurance issues.”

Source: Pink Sheet 25 April 2017
OMQ Enforcement Actions* in 2016

- Import Alerts, 47
- Untitled Letters, 4
- Warning Letters Issued & Cleared, 54
- Regulatory Discretion, 27
- Regulatory Meetings, 27

*Excludes compounding-related actions

Source: "Compliance Trends, Paula Katz, Director, Manufacturing Quality Guidance and Policy Staff, OMQ, CDER
Recent Warning Letter Trends (Chart)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Integrity</td>
<td>19</td>
</tr>
<tr>
<td>Supply Chain</td>
<td>3</td>
</tr>
<tr>
<td>Sterility Assurance</td>
<td>7</td>
</tr>
<tr>
<td>Rudimentary CGMP</td>
<td>20</td>
</tr>
<tr>
<td>Delay/Deny/Limit/Refuse</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: “Compliance Trends, Paula Katz, Director, Manufacturing Quality Guidance and Policy Staff, OMQ, CDER

Will FDA Issue an Import Alert?

IA 66-40 or 99-32 if:

- CGMP violation could cause drug quality defect with potential adverse patient health consequences
- Repeat violations
- Significant data integrity violations
- Delay, denial, refusal or limitation of inspection

Source: “Compliance Trends, Paula Katz, Director, Manufacturing Quality Guidance and Policy Staff, OMQ, CDER
2. Failure to prevent unauthorized access or changes to data and failure to provide adequate controls to prevent manipulation and omission of data.

During the inspection, our investigators discovered a lack of basic laboratory controls to prevent changes to and deletions from your firm’s electronically-stored data in laboratories where you conduct CGMP activities. Specifically, audit trail functionality for some systems you used to conduct CGMP operations was enabled only the day before the inspection, and there were no quality unit procedures in place to review and evaluate the audit trail data. For example, you used standalone HPLC (2-RD HP/SM/32) to conduct analyses for Drug Master File (DMF) submissions and investigations, such as characterization of a starting material for your (b)(4) DMF. You also used uncontrolled systems to conduct out-of-specification (OOS) investigations for in-process materials used to manufacture (b)(4) API.
3. **Limiting access to or copying of records**

Your firm limited access to or copying of records that our investigators were entitled to inspect. For example, our investigators requested records of your audit trail data from all chromatographic systems used to test drugs for the U.S. market at your facility. The files you ultimately provided (in the form of Excel spreadsheets rather than direct exports from your chromatographic software) were not the original records or true copies, and showed signs of manipulation. The records you did provide contained highlighting, used inconsistent date formats, and lacked timestamp data; these features are inconsistent with original data directly exported from chromatographic testing software.

Our investigators and their supervisor explained at least twice that the data you provided was not representative of actual audit trail data from the chromatographic systems, and requested that you provide the original, unmodified records. **Your firm stated, without reasonable explanation, that you could not provide the requested audit trail records.** When our investigators explained that your failure to provide the requested records would be documented as **refusal,** you acknowledged the **refusal.**
Import Alert 66-40 “Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs”

Import Alert 99-32 “Detention Without Physical Examination of Products From Firms Refusing FDA Foreign Establishment Inspection”

Protocol for Oversight of Quality of Drugs Offered for Importation

- Each batch/lot of each drug offered for importation to the U.S. should have release testing conducted by an independent laboratory per the drug’s established specifications.
- An independent auditor with appropriate CGMP expertise, including knowledge of electronic data systems and analytical testing, should certify that all test results and related raw data for each batch/lot of each drug offered for importation into the U.S, has been reviewed, verified and found to be acceptable.
- Any discrepancies detected by the independent auditor shall be thoroughly investigated and a summary investigation report be provided to FDA.
- The auditor’s certification will be submitted to FDA for each batch/lot of each product offered for importation into the U.S.
WHO's Position on the Import Alert for a Chinese API Manufacturer's Products

Qinhuangdao Zizhu Pharmaceutical, Co. FDA WL 4/24/17

- Handling of data in the area of quality control (data manipulation, audit trail feature disabled, missing access controls, repeated analyses until the desired results be achieved)

- Inappropriate exercising of the QC's responsibilities with regard to the release of products (incompletely filled in, unapproved batch records).

- The Warning Letter presents an impressive list of 17 items criticized and required by the FDA.

WHO Prequalification Team (PQT) had inspected Qinhuangdao Zizhu Pharmaceutical in October 2015 for levonorgestrel, mifepristone and ethinylestradiol APIs.

- 5 major deficiencies including data integrity issues and several minor deficiencies.

- CAPAs for all deficiencies; the inspection was closed as compliant based on the CAPAs provided by the manufacturer.

“No alternative levonorgestrel API which has been prequalified by WHO-PQT. Until further notice, procurement agencies may continue to procure FPPs that contain API produced at Qinhuangdao Zizhu Pharmaceutical.” (Source: https://extranet.who.int/prequal/news/who-response-usfda-import-alert-issued-qinhuangdao-zizhu-pharmaceutical-co-ltd-active)
Evolution of Expectations & Enforcement Activity
211.180 General Requirements
(e) Written records maintained and reviewed, at least annually
(f) If not personally involved or immediately aware, responsible officials of the firm are to be notified in writing of investigations, recalls, inspectional observations, or regulatory actions

Originally proposed to require routine quarterly written reports because FDA believed “corporate officials have not been advised of potential or real adverse conditions brought to light either by the firm’s own quality system or FDA.”

Industry objected “on the basis that it is an unwarranted intrusion into corporate duties and responsibilities.”

FDA’s Response: “In view of the comments, however, the Commissioner is deleting the proposed requirement regarding routine quarterly written reports in order to allow manufacturers flexibility in establishing procedures to keep appropriate management fully informed as to important matters involving possible quality control problems.”
Submission of Quality Metrics Data
Guidance for Industry

DRAFT GUIDANCE
Kopcha said that "I really was hoping is that we would get some constructive feedback that would help us move quality metrics forward. We didn't really get what we had hoped for. It's OK. We're going to still deal with it anyway."

He went on to remind the audience that FDA needs to surveil the industry, identify quality-related trends and press for mitigation where needed to prevent drug shortages.

"I know a number of individuals have looked at quality metrics and been concerned that we're trying to figure out where we can maybe write more 483s or figure out if there's some nefarious things going on behind the scenes. But really it's for us to drive better quality in the pharmaceutical industry."
“Indian firm's invalidated out-of-specification rate was too high, FDA suggests in heavily redacted Form 483 report. This rate, which also came up in two recent warning letters, happens to be one of the three rates the US Agency wants to use as quality metrics for deciding how soon investigators should revisit sites.”
OBSERVATION 1
There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,
Your firm has invalidated 87% of the OOS for [REDACTED] used in [REDACTED] from 2015 to 2017. For example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

From January 1 to June 30, 2016, your firm invalidated 101 out of 139 (about 72 percent) initial out-of-specification (OOS) assay results without sufficient investigation to determine the root cause of the initial failure.
2. 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)).

Your records showed that multiple in-process and finished batches of fluticasone propionate nasal spray USP failed assay for (b)(4). For example, in-process batches (b)(4) and (b)(4) initially failed release criteria for (b)(4), as did their respective finished product batches (b)(4) and (b)(4).

When our investigator reviewed your investigation into these initial (b)(4) failures, we found that your investigation protocol (b)(4) assigned the cause of the failures to analyst error if repeat tests delivered passing results. The original results were invalidated without scientific justification under the protocol and only re-test results were reported as part of batch release decisions. The original results were not reported or considered in evaluating the quality of your drugs for release.

In response to this letter:

• Retrospectively review every instance where you did not conduct in-process testing at the appropriate time.
• List all OOS, invalidated OOS, unexpected, and out-of-trend (OOT) in-process test results for products within expiration.
• Investigate your previous assessments of the quality standards of each drug product to determine the need for changes in drug product specifications, manufacturing, or control procedures as required by 21 CFR 211.180(e).
1. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

Your quality control unit did not have basic controls to prevent changes to your electronically-stored laboratory data. Your analysts had user privileges to the Empower-2 system used to generate and analyze chromatographic data that allowed them to eliminate failing, atypical and satisfactory results with no notification; alter peak areas; and add or eliminate samples from sequences without authorization.

During the inspection, we reviewed an audit trail from your Empower-2 system that stored 8,906 entries. Of these, well over half indicated some form of data deletion or manipulation, including at least 1,441 instances of deleted results, at least 3,643 instances of manual integration, and at least 194 instances of altered running sample sets. Your personnel confirmed that these actions are common during chromatographic data processing. We found that you did not have a procedure in place to indicate the requirements and level of restrictions for users of the automated system.

2. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

Your laboratory procedures allowed analysts to modify chromatographic sequences and delete results with no justification.

During our review of chromatograms generated during impurities testing for (b)(4), we observed that your analysts conducted many manual integrations. We also found discrepancies in peak integrations, including inconsistent integrations, and peaks that were not integrated at all. Such peaks could represent impurities: they were not included in data packages presented to your quality unit for batch release decisions. Therefore, your quality review and product release decisions were based on incomplete data regarding the quality of your drugs.
Mutual Recognition
• "The European Medicines Agency says it will make efforts to defer any good manufacturing practice inspections in the US in anticipation of the EU-US mutual recognition agreement coming into operation from Nov. 1 onwards."

• EMA to have completed its assessment of FDA by July 1, 2017

• FDA needs to assess inspection capabilities of at least 8 EU member states by Nov 1, 2017 and assess all member states by July 15, 2019
Major Deliverables

- Mar 2017: Letters exchanged
- Jul 2017: EU completes FDA assessment
- Nov 2017: FDA completes 8 assessments
- Nov 2017: Recognize inspections
- July 2019: FDA completes all assessments
- Determine inclusion of other products

FDA Registered Drug Facilities
2011

6,877 FACILITIES

957 FACILITIES

453 FACILITIES

435 FACILITIES

United States

European Union

China

India

Potential FDA-EU Inspectorates

CHINA

INDIA

Mutual Recognition Q&A

• EMA:

• FDA:
The objective of the document is to:

- ensure that a standardized procedure is followed for desk assessment of inspection reports issued by trusted, competent regulatory bodies and corrective actions from inspected sites;
- to facilitate a convergent approach and model for exchange and use of inspection information in national and regional decision-making processes concerning the necessity to perform preapproval and surveillance inspections.