Securing the Supply Chain: Combating evolving risks in drug sourcing & manufacturing

Dinesh S. Thakur
Executive Chairman
• Set the context: How important is the Chinese pharma industry to the US market?
• What lessons can we learn from what has happened to the Indian pharma industry?
• What can the industry in China do to avoid a situation like India?
• How is the US FDA looking at product quality?
  – What does it mean for the industry?
• Q&A
Setting the context: Importance of China to the US

Top 12 source countries for U.S. imports of pharmaceuticals and medicines by weight (kg) from 1992 to 2009

Top source countries for U.S. imports of ibuprofen, acetaminophen and aspirin by weight (kg) in 2009

Source: The Pew Charitable Trusts

Source: U.S. Census Bureau, Foreign Trade Division.
Trends affecting the pharma industry in India

Percentage of Respondents who would consider outsourcing to CROs/CMOs in Emerging Markets

Percentage of Outsourced Projects assigned to India

Importance of the US market to Indian companies

Figure 5: Indian players’ US revenue grew from $600 to $4.5b in seven years

Source: Companies, IIFL Research

Figure 1: The US has become the largest business by far for large Indian pharma

Source: Companies, IIFL Research
Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA

In the largest drug safety settlement to date with a generic drug manufacturer, Ranbaxy USA Inc., a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Limited, pleaded guilty today to felony charges relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy’s manufacturing facilities in India, the Justice Department announced today. Ranbaxy also agreed to pay a criminal fine and forfeiture totaling $150 million and to settle civil claims under the False Claims Act and related State laws for $350 million.
Offenses of Conviction

1. The Defendant agrees to knowingly and voluntarily waive indictment and plead guilty to Counts One through Seven of a criminal information to be filed against it, which will charge it with introduction into interstate commerce of adulterated drugs, with intent to defraud or mislead, in violation of 21 U.S.C. §§ 331(a), 333(a)(2), and 351(a)(2)(B); failure to timely file required reports with intent to defraud or mislead, in violation of 21 U.S.C. §§ 331(e) and 333(a)(2);
Ranbaxy knowingly manufactured, distributed, and sold in interstate commerce, and made false statements (including in annual reports to the Food and Drug Administration) about, certain batches, lots, or portions of lots of the Covered Drugs during the period referenced above in violation of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 331, 351, 352, and 355, including batches, lots, or portions of lots of the Covered Drugs (1) the strength of which materially differed from, or the purity or quality of which materially fell below, the strength, purity, or quality which they purported or were represented to possess, or (2) that were not manufactured according to the approved formulation and were, therefore, unapproved new drugs, in violation of the FDCA, 21 U.S.C. §§ 331(d) and 355(a), and were not “covered outpatient drugs” under 42 U.S.C. § 1396r-8(k)(2).
Impact of FDAsia

Establishment Inspections by US FDA

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India has a systemic problem

Approximately 90% of Indian pharma companies faced
issues under these categories between 2006-12

<table>
<thead>
<tr>
<th>Severity: High</th>
<th>Severity: Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hygiene Standards</td>
<td>Procedural Awareness</td>
</tr>
</tbody>
</table>

**Examples:**
- Failed to establish appropriate written procedures designed to prevent microbial contamination
- Failed to maintain buildings in a clean and sanitary condition
- Failed to provide adequate washing and toilet facilities to employees

- Failed to ensure that each person engaged in the manufacturing and handling of the drug product has necessary education, training and experience
- Laboratory records did not include complete data derived from all tests necessary to assure compliance with established specifications & standards
- Failed to thoroughly investigate any unexplained discrepancy of a batch to meet any of its specifications
- Failed to follow required laboratory control mechanisms and to records and justify any deviations
- Failed to protect computerized data from unauthorized access or changes
- Testing into compliance
- Creating false ECGs
- Repeatedly delayed, denied, limited an inspection or refused to permit the regulatory inspection
- Data inconsistencies: Person reported as supervisor for the operation not present on the dates the operation was conducted

**Data represents enforcement actions faced by Indian pharmaceutical companies**

**Source: CRISIL**

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Compliance with cGMP is a key priority for the US

# of FDA inspected Mfg Facilities (2013)
Physicians are beginning to ask questions

**Generic Versions of Toprol XL, a Heart Drug, Are Recalled**

By KATIE THOMAS  JUNE 23, 2014

For years, Dr. Harry Lever, a cardiologist at the Cleveland Clinic, has been warning nearly anyone who would listen of his growing suspicions about generic versions of a widely used heart drug, Toprol XL.

Patient after patient, he said, would visit his office complaining of chest pains or other symptoms after switching from the brand-name version, made by AstraZeneca, to a generic product, often one made in India. When he switched them back to the brand — or to another generic — the symptoms disappeared, he said. Dr. Lever wrote a letter outlining his concerns to the Food and Drug Administration in 2012, and this year, he traveled to Washington to try to get the attention of Congress.

Dr. Lever could not prove that the generic drugs were to blame. “You see enough people and you get a feel, but it’s anecdotes,” he said in an interview Monday. “It’s not science.”

NY Times, June 23, 2014
What does this mean for China?

Source: Thompson Reuters
What does this mean for China? (2)

Filler in Animal Feed Is Open Secret in China

ZHANGQIU, China, April 28 — As American food safety regulators head to China to investigate how a chemical made from coal found its way into pet food that killed dogs and cats in the United States, workers in this heavily polluted northern city openly admit that the substance is routinely added to animal feed as a fake protein.

Recalls Under Consumer Product Safety Commission Jurisdiction
By Country or Administrative Area of Manufacture, 2002-2013

<table>
<thead>
<tr>
<th>Country</th>
<th># of inspections</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>111</td>
</tr>
<tr>
<td>China</td>
<td>111</td>
</tr>
<tr>
<td>Germany</td>
<td>71</td>
</tr>
<tr>
<td>Canada</td>
<td>46</td>
</tr>
<tr>
<td>France</td>
<td>43</td>
</tr>
<tr>
<td>Italy</td>
<td>49</td>
</tr>
<tr>
<td>Japan</td>
<td>47</td>
</tr>
<tr>
<td>Switzerland</td>
<td>36</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>33</td>
</tr>
</tbody>
</table>

Source: US FDA, FY 2014

Our customers see this clearly

<table>
<thead>
<tr>
<th>Percentage of respondents</th>
<th>Importance</th>
<th>Performance</th>
<th>Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leverage contract manufacturers for successful new product launch, lower costs and agile response to demand</td>
<td>53</td>
<td>29</td>
<td>-24</td>
</tr>
<tr>
<td>Better use of technology to drive down costs and enhance productivity</td>
<td>54</td>
<td>23</td>
<td>-31</td>
</tr>
<tr>
<td>Develop a supply chain vision supported by governance and change management processes to guide execution of supply chain priorities</td>
<td>61</td>
<td>31</td>
<td>-31</td>
</tr>
<tr>
<td>Develop value chain strategies versus functionally siloed supply chain capabilities</td>
<td>61</td>
<td>24</td>
<td>-37</td>
</tr>
<tr>
<td>Ability to forecast demand accurately and respond quickly to changes in demand</td>
<td>66</td>
<td>25</td>
<td>-41</td>
</tr>
<tr>
<td>A balanced S&amp;OP (Sales and Operations Planning) processes which profitably matches demand and constrained supply</td>
<td>64</td>
<td>19</td>
<td>-42</td>
</tr>
<tr>
<td>Develop effective supply chain capabilities in emerging markets</td>
<td>75</td>
<td>2</td>
<td>-46</td>
</tr>
<tr>
<td>Achieve compliant, predictable product supply by manufacturing right-first-time</td>
<td>69</td>
<td>31</td>
<td>-44</td>
</tr>
<tr>
<td>Align manufacturing, supply chain, sales and marketing and regulatory interaction for profitable operations and driving value to customers</td>
<td>69</td>
<td>23</td>
<td>-46</td>
</tr>
</tbody>
</table>

Observations in during US FDA inspections

- Records and Reports
- Organization and Personnel
- Production and Process Controls
- Equipment
- Laboratory Controls

- Resp. of QC unit
- Equipment cleaning and maintenance
- Lab Controls - general requirements
- Production record review
- Written procedures, prod. Process controls
### Top 5 observations on form 483 in 2014 for drugs

<table>
<thead>
<tr>
<th>Number of observations</th>
<th>Short description</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>Procedures not in writing, not fully followed</td>
</tr>
<tr>
<td>109</td>
<td>Lack of scientifically sound laboratory controls</td>
</tr>
<tr>
<td>94</td>
<td>Lack of proper investigations of discrepancies, failures</td>
</tr>
<tr>
<td>87</td>
<td>Absence of written procedures</td>
</tr>
<tr>
<td>72</td>
<td>Written procedures not established / followed AND Inadequate procedures for sterile drug product testing</td>
</tr>
</tbody>
</table>
## Remediation cost and revenue loss

<table>
<thead>
<tr>
<th>Company</th>
<th>Timing</th>
<th>Scope</th>
<th>Impact</th>
<th>Cost / Penalty</th>
</tr>
</thead>
</table>
| Generics Co.             | 2012 - current | Manufacturing and cGMP; data integrity issues; US and India facilities | Relinquished 180 day exclusivity for three ANDA applications             | • $500M in civil and criminal penalties  
                            |             |                                                      |                                                                         | • Up to $10M/year penalty if drugs are distributed from Consent Decree sites  
                            |             |                                                      |                                                                         | • Up to $30M/year penalty if additional untrue statements are made           |
| Consumer Healthcare Co   | 2011 - current | Three plants in Pennsylvania and Puerto Rico         | Product withdrawal & shortages; loss of market share                     | • $15K/day for missed commitments  
                            |             |                                                      |                                                                         | • $15K for each additional violation  
                            |             |                                                      |                                                                         | • Up to $10M files annually  
                            |             |                                                      |                                                                         | • Significant lost sales and incremental costs                              |
| Biotech Co               | 2010 - current | Fill/finish facility with contamination & cGMP issues | Company to recondition sized drugs                                       | • Consent Decree signed in Q1 2010  
                            |             |                                                      |                                                                         | • $175M disgorgement paid in Q4 2010  
                            |             |                                                      |                                                                         | • $15K/day for missed deadlines                                              |
| Pharma Co                | 2005 - current | cGMP violations and manufacturing issues             | Company to recondition sized drugs                                       | • $650M bond posted pending result of reconditioning                      |
| Pharma Co                | 2000 – 2006 | Two facilities in NY and Pennsylvania                 | Sites remained open with 3rd party oversight; one of the plants was sold | • $30M in disgorgement penalty & $26 million in other fees                
                            |             |                                                      |                                                                         | • $267M in fines paid                                                        
                            |             |                                                      |                                                                         | • Closure of two plants                                                       |
| Pharma Co                | 2002 – 2007 | Facilities in Puerto Rico and NJ                     | Sites remained open with third party oversight                             | • $500M disgorgement penalty  
                            |             |                                                      |                                                                         | • Potential for additional $175M fines if timelines are missed               
                            |             |                                                      |                                                                         | • $40M in lost sales due to termination of some product lines. Approval of delayed for > 1yr |
**Impact of (poor) Quality on top and bottom line**

- **Cost of quality events**
  - Cost of quality event:
    - Recall: $2M
    - Warning Letter: $1M
    - Consent Decree: $400M
    - 483 Obs: $0.1M

- **No. of quality events per year (2013)**
  - Recall: 60
  - Warning Letter: 43
  - Consent Decree: 3
  - 483 Obs: 3,527

- **Cost of major quality events**
  - Range of impact: $90 to $130M
  - Frequency: 10 to 20 events/year

- **Revenue impact of quality events**

- **$1.7 B**

- **$1 - $2 B**

- Supply chain risk events are the second largest contributors of large monthly declines in share price.
- Between 2000 and 2010, an average of one major quality event per year that resulted in a 13% stock price drop across the industry.

Source: FDA, McKinsey, Factiva
India and China have a significant cost advantage

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Labor Cost ($/operation/year)</th>
<th>Labor Productivity ($/employee/year)</th>
<th>Ratio</th>
<th>US</th>
<th>US =1</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>55,000</td>
<td>275,000</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>70,000</td>
<td>350,000</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>6,000</td>
<td>100,000</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>4,500</td>
<td>80,000</td>
<td>18</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Fine Chemical Industry Labor Cost & Productivity comparison, 2010
Source: US Bureau of Labor & Statistics
What it takes to achieve cGMP compliance

Big Pharma | Western CMO | India | China
---|---|---|---
10,000 | 1,000 | 300 | 150
5,000 | 300 | 150 | 50
Increased outsourcing has led to increased risk

<table>
<thead>
<tr>
<th>Percent of Cost of Goods</th>
<th>Risk Percentage</th>
<th>Weighted Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>60</td>
<td>19.23</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>34.62</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>46.15</td>
</tr>
</tbody>
</table>

If the relative risks of the three sources of manufacturing remain the same, then the overall risk exposure increases significantly.

Note: Based on manufacturing and sourcing data from 30 large and mid-size pharma companies

There is increased risk management – from earlier detection through risk mitigation.
Selection criteria for establishment inspections

**The Old Way**

**Site Ranking**

**Product & Process Factors**
- FACTS Product List & OASIS Imports
- FACTS Products List

**Facility Factors**
- Establishment Type
- Establishment Size
- Inspection Outcomes
- Recall Events
- Time since last inspection

**Product Codes** are used to determine which products are CDER regulated (Subclass code)

**Process Indicator Code (PIC)** part of the product code used to score products, e.g., A= Prompt Release Tablets, K= Sterile Liquid

**Establishment Type**: Manufacturers, Repackers, Control Labs etc.

**Establishment Size**: Proxy for measuring exposure

**History of inspection outcomes**: NAI, VAI or OAI

**Number of recalls in last three years**: Class I, Class II, Class III
• Risk Factors: In establishing the risk-based scheduled under paragraph (3), the Secretary shall inspect establishments according to the known safety risks of such establishments, which shall be based on the following factors:
  • Compliance history of the establishment
  • The record, history and nature of recalls linked to the establishment
  • The inherent risk of the drug manufactured, prepared, propagated, or compounded at the establishment
  • The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 with the last 4 years
  • Whether the establishment has been inspected by a foreign government or an agency of a foreign government under section 809
  • For any other criteria deemed necessary and appropriate by the Secretary for the purposes of allocating resources
Selection criteria for establishment inspections

The New Way

Inherent Product Risk Factors
- Drug Product Failures
  - Product Code
  - NDC Product
  - Unit Ops
- Unit Dose Consequence
  - Route of Admin
  - Therapeutic Class
- Exposure
  - Volume by Product

Facility Factors
- Quality Metrics
- Hazard Signals
- Compliance History
- Facility Demographics
  - Estab. Type
  - Estab. Age
  - Estab. Size

Drug Product Failures
- Process, Analytical, Sterility, API, Excipients, Stability, CMC, QC, QA, Batch Release, OOS, CAPA ...

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8 Pillars of an effective Quality System

- Science based approach
- Decisions driven by understanding of the intended use of the product
- Identification and control of potential process weaknesses
- Responsive investigative systems leading to timely remediation
- Sounds methods for assessing and reducing risk
- Well defined processes throughout the lifecycle
- Systems for careful monitoring of product quality
- Supportive management: Philosophically & financially

Source: Guidance for the industry: Quality systems approach to Pharmaceutical cGMP Regulations, 2006
<table>
<thead>
<tr>
<th>Beliefs &amp; Behaviors</th>
<th>Quality &amp; Compliance indicators</th>
</tr>
</thead>
</table>
| **Belief**  
*Cost efficiencies through operational excellence*  
**Behavior**  
*Financial targets are addressed through continuous improvement initiatives*  
**Belief**  
*Deviations are learning experiences to address root causes that can compromise operational excellence*  
**Behavior**  
*Investigate to identify and correct root cause vs. investigate to release the lot*  
**Belief**  
*Deviations are learning experiences to address root causes that can compromise operational excellence*  
**Behavior**  
*Investigate to identify and correct root cause vs. investigate to release the lot* |  
• Reduction in waste/scrap  
• Improved cycle times  
• Efficiencies in operational cost  
• Right first time  
• Deviation metric- reduction of repeat deviations  
• CAPA effectiveness  
• # of on-going Continuous improvement initiatives |
# Beliefs & Behaviors

## Belief
*Our primary responsibility is to our customers, consumers and patients*

## Behavior
*Market surveillance activities do not compete with making and releasing lots to market*

*Defining own internal standards vs. merely complying to FDA requirements*

## Quality & Compliance indicators

- Review, investigation and management of customer complaints executed in a timely manner
- Timely reporting to FDA and market action when required.
- On time stability testing
- Critical to quality process parameters are well defined and monitored
- Risks are known and mitigation plans are in place
- Reduced number of market actions

## Belief
*Management views product quality as a business imperative.*

## Behavior
*Management gets involved and seeks to understand site challenges through governance forums*

Product quality issues/constraints become business priorities and are resourced to be addressed in timely manner, favorably impacting:

- Product approval rate
- Customer complaint rate
Elements of Data Integrity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate</td>
<td>No errors or editing without documented amendments</td>
</tr>
<tr>
<td>Attributable</td>
<td>Who acquired the data or performed an action and when?</td>
</tr>
<tr>
<td>Available</td>
<td>For review and audit or inspection over the lifetime of the record</td>
</tr>
<tr>
<td>Complete</td>
<td>All data is present and available</td>
</tr>
<tr>
<td>Consistent</td>
<td>All elements of the record, such as the sequence of events, follow on and are dated or time stamped in expected sequence</td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>Documented at the time of the activity</td>
</tr>
<tr>
<td>Enduring</td>
<td>On proven storage media (paper or electronic)</td>
</tr>
<tr>
<td>Legible</td>
<td>Can you read the data?</td>
</tr>
<tr>
<td>Original/Reliable</td>
<td>Written printout or observation or a certified copy thereof</td>
</tr>
<tr>
<td>Trustworthy</td>
<td>The data and the record have not been tampered with</td>
</tr>
</tbody>
</table>

Breaches of data integrity (BDI) are acts of “falsification, document adulteration, forgery and providing misleading information” - Carmelo Rosa, Director, CDER Office of Compliance*


Source: R.D. Mcdowall, Spectroscopy, Focus on Quality, December 2010
## Data Integrity – Best practices

<table>
<thead>
<tr>
<th>Ensuring Data Integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embed data integrity verification activities into internal audit processes</td>
</tr>
<tr>
<td>Create awareness among staff so they can assist with this endeavor, and report concerns before they become full-fledged issues</td>
</tr>
</tbody>
</table>
Quality control at Chinese manufacturers

- There is much reliance on testing the product according to the pharmacopeia
- Testing is not always suitable to the manufacturing process, as pharmacopoeias cannot keep up with new processes
- Residues of solvents and potentially genotoxic catalysts are rarely controlled
- Impurity profiles are seen in only 6% of our audits

Source: Supervision of Chinese-made drug substance, Philippe Andre, Qualiau Pharmaceutical Auditing Co., Ltd.
Thank you

www.medassurecompliance.com
Appendix
Data Integrity during active usage

Example Considerations:
- Have personnel been trained on good documentation and good data integrity practices
- How does the firm ensure that analysts enter ALL test data, not just the passing test results?
- For transcribed data, what verification processes are in place?
- When data is scanned, how does the firm ensure the evidentiary admissibility of the scan (e.g., “certified copy”)?
- Has the system been validated and under change control?
Data Integrity during active usage

Example Considerations:
• Did the firm verify computerized calculations prior to usage on the data?
• Does the firm claim to use “paper records only” but then actively use e-records to release batches, make safety and efficacy decisions, etc.?
• How does the firm ensure that previously recorded SUSAR data cannot be altered when reviewed?
Data Integrity during active usage

Example Considerations:
- Does the firm retain raw lab data/digital clinical source data along with context (e.g., metadata)?
- What were the process checks undertaken prior, during, and after clinical trial database lock? Transmittal to the sponsor?
- Does the firm have traceability on its complaint records to ensure that none of the data is left out of any later analysis (such as for an APR or QSMR) or when transmitted?
Data Integrity during active usage

Example Considerations:
• If the firm uses a storage vendor, is the vendor qualified?
• How often does the firm sample its long-term archives to ensure continuing storage suitability and prevent data deterioration?
• What controls does the firm have on retained record destruction to prevent inadvertent loss of required data?
• Does the firm have a digital media migration strategy?
Identifying “Data Integrity” issues

- HPLC processing methods (including integration parameters) and re-integrations are executed without a pre-defined, scientifically valid procedure.
- Testing samples unofficially, and not reporting all results obtained. Specifically, “test,” “trial” and “demo” injections of intermediate and final API samples were performed, prior to performing the tests that would be reported as the final QC results.
- “When weighing samples, reagents, and other laboratory materials, QC analysts write weight values on small pieces of paper, transcribe the values onto the analytical worksheets, and then destroy the original paper on which the weights are written.”
- Failure to review and investigate production and QC laboratory deviations.
Identifying “Data Integrity” issues

• Out-of-specification or undesirable results were ignored and not investigated
• Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APIs intended for US distribution
• During the inspection, management acknowledged that the some of the chromatograms observed were related to the practice of blending an API batch that failed to meet specifications with an API batch that passed specifications. The combined batch was retested and distributed using the new acceptable Quality Control results.
Identifying “Data Integrity” issues

• The audit trail function for the chromatographic systems was disabled at the time of the inspection
• Failure to protect computerized data from unauthorized access, changes, or deletion
  • No computer lock mechanism had been configured to prevent unauthorized access to the operating system
• QC laboratory personnel shared the same username and password for the operating systems and analytical software on each workstation in the QC laboratory