Develop and Implement
Contingency Plans to Better
Prepare for Unexpected Events

CBI’s Biopharmaceutical Forum on Clinical and
Commercial Supply Chain Excellence

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BioProcess Technology Consultants
www.bptc.com
The Food and Drug Administration is preparing to fine the biotechnology giant Genzyme for recent manufacturing problems and take a greater role in overseeing operations at the company’s factory in Boston, the company said Wednesday.

Genzyme’s announcement indicates that federal regulators have, in effect, lost confidence in the company’s ability to run its factories without supervision.

Fake Cancer Drug Found in U.S.

The maker of the widely used Avastin cancer therapy was found in the U.S. Swiss drug maker Roche said it is warning doctors, hospitals and patient groups that a counterfeit version of its widely used Avastin cancer therapy was found in the U.S. Jonathan Rockoff has details on The News Hub: AP

Swiss drug maker Roche said it is warning doctors, hospitals and patient groups that a counterfeit version of its widely used Avastin cancer therapy was found in the U.S.

Japanese Tsunami Has Global Effect on Supply Chains

The world is still reeling from the effects of the recent earthquake and subsequent tsunami in Japan, and experts say the worst may still be to come for many companies’ supply chains.

A wide range of manufacturing industries are feeling the pinch from disrupted supply chains.

It's a new kind of brinkmanship for U.S. doctors: caring for patients with life-threatening diseases when the supply of critical drugs threatens to disappear.

The most crisis concerns the old standby drug methotrexate. For six months, it has made the difference between life and death for children with acute blastic leukemia, or ALL, and a bone cancer called osteogenic sarcoma.

Hospitals around the nation are barely able to running out of a form of methotrexate that is necessary to inject patients.
Supply Chain Case Studies

- In January 2010, warning letter, FDA claimed employees at XiAn Libang Pharmaceutical Co., Ltd., in Shaanxi Province, China, manipulated testing data.
- In February 2010, Indian manufacturer Glochem found to have falsified batch-manufacturing records for clopidogrel, an antiplatelet medicine. E.U. inspectors discovered at least 70 batch-manufacturing records in the plant’s waste. All of the records had been re-written, and in some cases original entries had been changed.
- In 2008, FDA cited Indian manufacturer Ranbaxy Laboratories Limited for multiple U.S. GMP violations, including alleged falsification of stability testing records.
- One pharmaceutical auditor working in China observed during inspections and audits that for 39 percent of exported APIs, the final European or American customer was misinformed about the identity of the manufacturing site where all or part of the manufacturing took place.
Supply Chain Issues

All parts of the pharmaceutical supply chain are exposed to risks and potential disruptions

Source: Pew Health Group; After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs July 2011
Number of foreign establishments named in U.S. drug marketing applications more than doubled over an eight-year period\(^1\)


FDA Product Recalls

Data extracted from Recall Enterprise System 2012-Jan-05
Includes dietary supplements
Supply Chain Case (Horror) Studies (Stories)

Adulterated Product

- Cough Medicine
  - In 2006, Taixing Glycerin Factory in Hengxiang, China labeled barrels of diethylene glycol (DEG) as glycerin, a common excipient (inactive ingredient) used to make medicines into syrups
  - DEG is chemically similar to glycerin, but less expensive to make
  - Material passed through brokers in China and Spain, being relabeled at each step, before reaching Panama
  - The official number of deaths was 78, but unofficial reports suggest a much higher number

- Tamiflu
  - In 2010, counterfeit Tamiflu® was being sold online, originating in India
  - FDA determined that the active ingredient had been substituted with a material similar to penicillin which could cause severe reactions in allergic patients
Supply Chain Risk Management

1. Understand the risks and their potential impact

2. Decide on the organization’s “risk tolerance”

3. Make appropriate risk mitigation/recovery plans based on 1) and 2)

Stuff happens… how well prepared are you to deal with it?
Risk based approach – ICH Q9
- Assess risks, develop controls, conduct risk reviews, and communicate
  - What might go wrong
  - What is the likelihood (probability) it will go wrong
  - What are the consequences (severity)

Example: Natural Disasters
## Risk Ranking and Filtering

### Risk Ranking

<table>
<thead>
<tr>
<th>Probability</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Ranking</td>
<td>Risk Class ONE</td>
<td>Risk Class TWO</td>
<td>Risk Class THREE</td>
</tr>
</tbody>
</table>

### Severity

- **Low**
- **Medium**
- **High**

### Detection

- **HIGH priority**
- **MEDIUM priority**
- **LOW priority**

#### Risk Classification

- **One**
- **Two**
- **Three**

Segment risks according to potential impact on public health, brand reputation, and corporate finances.
Manage and Control Risk

- Signal detection
  - Geopolitical and weather events can be signals for a potential economically motivated adulteration
    - e.g. – melamine
  - Unusual complaint, adverse event
  - Unrelenting cost containment pressure

- Signal response
  - Develop plan commensurate with the risk
  - Include steps to assure a safe and continued supply
    - e.g. if risk is high for theft – change routes, add additional drivers/escorts, add covert tracking devices
    - e.g. if risk is high for adulteration – add additional testing
Exploring attitudes about risk related to
• Supplier & Raw Materials
• Manufacturing
• Contamination
• CMOs
• Disposables
• Demand Forecasting
• Inventory
• Distribution

Questions about
• Metrics
• Mitigation Strategies

Initiative in Research for Biopharmaceutical Products
Concern About a Variety of Risks

1: Not concerned  3: Concerned  5: Extremely Concerned
Limited Use of Modeling Tools

- **Actuarial Tables**: 14.5%
- **Value at Risk**: 36.8%
- **Failure Modes and Effects Analysis (FMEA)**: 71.9%
- **Monte-Carlo Modeling**: 26.3%
- **Discrete Event Modeling**: 29.8%
- **Other (please specify)**: 11.0%
73% Consider Forecast Error a Potential Risk, but…

How well do you explicitly model demand variability in your planning processes?

- 44.9%: We don't
- 18.0%: We model some upsides and downsides
- 7.3%: We use distributions to model percentiles of likelihood
- 29.8%: Other (please specify)
Key Survey Take-Away

- Generally high level of concern about...
  - Supplier risk
  - Manufacturing reliability
  - Catastrophic risk
  - Inventory levels
  - Cold chain
  - Forecast-related risks
  - Outsource capacity management
  - Lack of “global” or “system” view of risk

- But...
  - Little detailed analysis of relevant data
  - Little formal risk quantification
  - Little modeling of risk or risk mitigation strategies
  - Little inventory optimization – Focus on “more inventory”
  - Little measurement of uncertainty (of demand, for example)

Even though there is plenty of data available
Actions to Take

Develop contingency plans to better prepare for and address supply challenges resulting from an unexpected event.
Thoroughly Map Your Supply Chain

- Include all suppliers, manufacturing, storage, shipping lanes
- Map the flow of materials and information
- Identify high risk nodes and transition points where SC could be disrupted
- Know what contingencies are possible, e.g., inventory build, second sourcing, delayed differentiation
Evaluate Impact of Disruption

- How robust are your demand forecasts?
- Is redundant capacity an option? At what cost?
- Are there multiple suppliers / service providers available?
- What are the access hurdles for these suppliers / service providers?
- What visibility do you have into secondary and tertiary level suppliers?
- Can product be stock piled?
Supplier Quality Management

- Industry supplier qualification programs, quality agreements and life cycle monitoring are often deficient
- Supplier assessment and selection
  - Apply QRM principles appropriate for the material, e.g., raw materials versus drug product versus packaging material; geographic location; regulatory environment
  - Multi-disciplined approach leads to more balanced assessment of potential suppliers
  - Full extent of supply chain should be documented
    - Maintain info from 2nd and 3rd tier suppliers
    - Capture all risks identified during evaluation and risk controls required
      - Risk mitigation costs should be included to identify the true TOTAL cost
Supplier Quality Management

- Written agreements for quality activities
  - Quality/technical agreements, service/supply agreements, etc. should clearly document and communicate requirements and standards
    - Written agreements should define
      - Roles, responsibilities and communication processes
      - Required quality systems
      - Agreed upon supply chain
      - Expected controls
    - Minimum requirements should be established for
      - Notification of changes
      - Notification of deviations
      - Notification of inspections
      - Provisions for document review
      - On-site audits using risk based criteria
    - Review and revise agreements periodically
Performance Management and Access to Supply Chain Data

- **Supplier monitoring**
  - Set performance metrics and measure against them
- **Virtual manufacturers** will need to ensure they have access to reliable data from every stakeholder in their supply chains
  - Most pharma companies rely on periodic audits, but these only produce snapshots in time
  - Most companies can’t get vital supply-chain data rapidly
- **Encourage suppliers to develop better understanding of key parameters and implement process controls to produce greater supply chain visibility**

Challenging to get information from critical suppliers and distributors within two hours

Source: PWC Pharma 2020 Supplying the Future
Scenario Planning

Sources of Uncertainty that Can Cause SC Disruption

- Forecasting – Monte Carlo simulations
- Geopolitical – keep up with local events
- Natural disaster – volcanoes
- Regulatory – Consent decree
- Counterfeiting / adulteration – Herceptin
Counterfeiting

Authentic Avastin

Counterfeit Avastin

Implementing a holistic and comprehensive supply chain risk management program can deliver a wide range of benefits, enabling companies to:

- Understand the likelihood of certain risks resulting in supply chain disruption
- Proactively and cost efficiently mitigate those risks
- Obtain incremental value by making risk-informed strategic supply chain decisions before the disruption occurs.
Thank You!

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Back-up
## Supply Chain Risk Management

<table>
<thead>
<tr>
<th>Supply Chain</th>
<th>Supply Chain Phase</th>
<th>Supply Chain Security Key Attribute</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Materials/Components</td>
<td>Sourcing</td>
<td>SC Transparency and Supplier Management</td>
<td>Supply and Quality Agreement Standards, oversight and supplier selection</td>
</tr>
<tr>
<td>Internal Mfg</td>
<td>Production</td>
<td>Packaging technology and manufacturing controls</td>
<td>Tamper-evident</td>
</tr>
<tr>
<td>External Mfg</td>
<td>Logistics</td>
<td>Warehousing and cargo security</td>
<td>Standards, oversight and supplier selection</td>
</tr>
<tr>
<td>Transportation</td>
<td></td>
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<tr>
<td>Warehousing</td>
<td></td>
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<tr>
<td>Distributor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provider</td>
<td>Market</td>
<td>Market monitoring and product integrity</td>
<td>Surveillance, investigation, advocacy and market education Product integrity/authentication</td>
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<tr>
<td>Consumer</td>
<td></td>
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<td></td>
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</tbody>
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<thead>
<tr>
<th></th>
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<th>Production</th>
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<th>Market</th>
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</thead>
<tbody>
<tr>
<td><strong>Robust agreements</strong></td>
<td></td>
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<tr>
<td><strong>Risk and security assessment upfront</strong></td>
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<td></td>
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<tr>
<td><strong>Prevention</strong></td>
<td>Material qualification</td>
<td></td>
<td>Conveyance standards</td>
<td>Supply controls</td>
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<td></td>
<td></td>
<td></td>
<td>Shipment value limits</td>
<td>Sample management</td>
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<td></td>
<td></td>
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<td>Reverse logistics</td>
</tr>
<tr>
<td><strong>Detection</strong></td>
<td>Inspection and testing</td>
<td>Serialization</td>
<td>Auditing</td>
<td>Market intelligence</td>
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<tr>
<td></td>
<td>Auditing</td>
<td>Surveillance testing</td>
<td>Tracking systems</td>
<td>Complaint handling</td>
</tr>
<tr>
<td></td>
<td>Market intelligence</td>
<td>Auditing/oversight</td>
<td>Return goods policy</td>
<td>Authentication testing</td>
</tr>
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<td></td>
<td></td>
<td>Reg licensing</td>
<td></td>
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<tr>
<td><strong>Response</strong></td>
<td>Continuous improvement</td>
<td>Exit strategies</td>
<td>Reg, law enforcement</td>
<td>Enforcement</td>
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<td></td>
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<td>collaboration</td>
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