

Index

1	INTRODUCTION	2
2	MAIN ISSUES	2
2.1	Regulatory Compliance	2
2.2	Product Supply Interruptions	2
2.3	Cost of Interruptions	4
3	RISK MANAGEMENT	4
4	QUANTIFICATION OF SUPPLY CHAIN THREATS	5
4.1	Benefits	5
5	HOW TO IMPLEMENT SCAIR™	6
6	ABOUT THE AUTHORS	6
7	WORKS CITED	7

1 Introduction

Those of us who have worked in life sciences, manufacturing or supplying services, will all have experienced a supplier failure at sometime, probably more than one. These can have a minor impact on our business or they can have a more far reaching impact on our ability to deliver our drugs and services and on our reputation and income.

As a highly regulated industry we should understand the requirements for supplier qualification, materials qualification, audit and ongoing monitoring of material quality and supplier performance. These measures are designed to ensure quality of product impacting materials used in the manufacture of our products or delivery of our services.

However, how well do we understand the impact of supply failure on our business? Do we understand how many product lines might be affected? Have we lost sight of, or have we never known the consequence of interruption of our

supplies of something as simple as sodium chloride? Do we focus only on the high profile product and forget our core ones?

Do we know the impact on our bottom line?

These are important issues not just for procurement and quality management specialists but critically for the Management Team and ultimately business governance and shareholder value.

2 Main Issues

2.1 Regulatory Compliance

Despite being highly regulated, pharmaceutical companies are still having problems complying with accepted regulatory practice for controlling suppliers and materials.

A recent presentation which reviewed deficiencies identified by the MHRA during 291 inspections conducted between April 2009 and March 2010⁽¹⁾, found that 187/1368 (14%) observations related to materials management and of these 187, 82 (44%) related to problems in supplier/contractor audit and Technical Agreements. A further 56 observations (30%) related to non compliance to TSE guidelines and an inability to demonstrate that an API had been manufactured to GMP. Should any of these have led to a cessation of manufacture of a product using the API or suspension of a supplier pending resolution of supplier audit/agreement issues then it is highly likely that a supply interruption would have arisen.

2.2 Product Supply Interruptions

As of the 29th March 2011 there were a total of 51 drug shortages reported in the USA by the FDA⁽²⁾. Shortages can take anywhere from several months to more than a year to resolve. Commodity shortages, material quality problems or change of contract manufacturer accounted for 4/54 (7%) of the reported shortages. Case 1 resulted from an unplanned event which affected one of only 5 reactors across the world providing the materials required for the manufacture of radiopharmaceutical products along with a contemporaneous, unavoidable but planned

shutdown in a second major supplier of these materials.

Case 1 ^{(10) (9)}

Technetium-99m (Tc-99m) Radiopharmaceutical Product Shortage

- ***Used in approximately 80% of radiopharmaceuticals***
- ***18 month worldwide shortage***
- ***Caused by an unplanned interruption in supply from one reactor along with a contemporaneous planned shutdown for maintenance in a second reactor***

Impact: Shortage of products used in nuclear medicine imaging and diagnosis

Case 2 also had a wide ranging and substantial impact on the pharmaceutical industry. Back in 2007 Shin Etsu supplied a significant proportion of the pharmaceutical industry's demand for methylcellulose – an excipient used in numerous formulations. With the alternative supplier in the US, DOW Chemical, struggling to meet the shortfall in capacity, there was a global scramble for capacity.

Case 2 ^(8; 11)

Methylcellulose (pharmaceutical excipient) shortage

- ***Explosion occurred in March 2007 at Shin-Etsu's Naoetsu Plant***
- ***Single sourced within the company only one other alternative provider of capacity (in US).***
- ***By October 2008 production levels were still only at 90% of production capacity prior to the incident.***

Impact: Global shortage of pharmaceutical grade celluloses that impacted major pharma's formulations worldwide.

Manufacturing delays in one or more supplier of a drug are described as being the cause of 32/54(58%) of the reported product shortages on the FDA list as at 29th March 2011 ⁽²⁾. The reason for these delays is often not described in detail.

However the FDA in a Question and Answer paper ⁽³⁾, prepared in response to a shortage of propofol (a sedative used for induction of anaesthesia or sedation (Case3)), described some of the major

factors that can lead to drug shortages. These included:

- Capacity and production lines being dedicated to multiple products. Therefore if a quality problem occurs in one product then often the whole line and therefore other products are affected.

Often it will take a number of months or more for other suppliers to ramp up capacity to compensate for a reduction in supply.

- Pharmaceutical supply chains do not typically have much excess inventory in the system. It appears that the inventory of finished products held by the manufacturers, wholesalers and pharmacies can be less than 1 month supply.

Case 3 ⁽³⁾

Propofol Anesthetic Product Shortage –Autumn 2009 Shortage caused by

- ***Two manufacturers (Teva and Hospira) developed quality problems and recalled products***
- ***The manufacturers continued to experience manufacturing difficulties***
- ***Eventually led to both companies withdrawing from the market at the same time, one has now returned***

Impact: Continuing shortage of propofol in USA.

The risks of interruptions to Life Science supply chains are believed to be greater during uncertain economic times according to a recent Price Waterhouse Cooper (PWC) KnowledgeLine paper ⁽⁴⁾. They cite difficulties in the ability of small biotechs to source funding as potential disruptor to their operations. They also report that small medium sized API manufacturers in China and India are experiencing falling orders leading to potential shrinkage of operations and closure of some businesses. Suddenly, as a result of financial problems, a company could find that a supplier downstream in their supply chain is no longer there.

Drug supply shortages clearly impact on patients. In some cases it is possible to switch patients to

alternative therapies but in others this is much more difficult to do especially for some of the newer drugs or where patients are in mid treatment. A huge amount of effort is required to manage supplies to make sure that the remaining product is reserved for such patients.

Clearly there can be considerable cost and loss of reputation and confidence associated with these types of events.

2.3 Cost of Interruptions

2.3.1 Cost of Recalls and Lost Revenue

The recent high profile interruption to supply of Genzymes products Cerezyme and Fabrazyme serve to illustrate the potential cost of supply interruption, in this case due to process problems rather than raw material interruption, in terms of cost of recalls, clean down costs (which alone cost around USD25 million) and loss of revenue⁽⁵⁾. Loss of revenue for these products for year ending 2009 was reported as USD 444.5 million⁽⁵⁾.

Johnson and Johnson reported in January 2011 that the annual cost of product recalls of Over the Counter (OTC) drugs for year ending 2010 was a staggering 900million USD⁽⁶⁾.

2.3.2 Impact of Supply Chain Interruptions on Shareholder Value

A study conducted by PWC⁽⁷⁾ which compared more than 75 pharmaceutical companies which experienced supply chain failures in 2007 with peers who did not, revealed the impact on shareholder value. Within the two day announcement period (the day before and day after a public announcement of a disruption) the share price in the affected companies fell by an average of 9% below their unaffected comparator group. PWC noted that the stock prices of two thirds of affected companies were still lagging behind their bench mark group a year later. Stock prices of affected companies were still underperforming their peers on average by 19% when comparing the price over a two year period (one year before and one year after) the disruption showing a continuing loss in confidence. Returns on assets and sales were also adversely affected on average 5% and 4% lower respectively compared to the benchmark group.

3 Risk Management

Given that there are real and present risks in supply chain management, be it failure to meet regulatory standards in managing suppliers, loss of supply due to quality failures or economic failure of a supplier, what can be done to address these?

Modern supply chains are complex and include raw materials, part manufactured goods, procured services and outsourced manufacturing and distribution. Few if any companies, especially in this age of 'virtual' companies, will have all supplies and resources under their direct control and must rely on third parties to deliver to the right quality, on time.

The principles of risk management need to be applied firstly by identifying and evaluating the risks i.e. focus on credible threats and quantify their impact on the business.

Once this has been done, decisions can be taken on the best options to take based on the costs of mitigation and the impact to the business. A company can

- Accept the risks and impact
- Reduce the impact down to tolerable levels
- Transfer the risks to third party
- Prepare financial plans to fund mitigating activity
- Put in place plans and identify resources to manage mitigation plans and plans to allow an organisation to manage an incident should it occur.

In terms of regulatory risks, these can be controlled for individual suppliers by

- Assessment of the impact of the material or service on the quality of products
- Careful vendor qualification
- Good technical agreements and contracts
- Ongoing vendor audit and monitoring of performance.

Other elements for controlling risk include

- development and maintenance of good business practices
- sound working relationships and communications
- development of market intelligence

It is important to understand things such as the

- financial wellbeing of suppliers,
- understanding the dependency of other companies on your supplier
- Whether your company is considered as a small customer relative to other customers which in turn could dictate who gets priority if the supplier has its own problems.

Market intelligence will help to provide information such as this which in turn will help in assessing risk in the supply chain.

Given that companies are likely to have numerous suppliers, this represents a considerable amount of data to collate in a meaningful way to analyse dependencies between product and service lines and the impact on the business should something go wrong with supplies to or from those lines.

This is where a systematic approach and a tool, that helps map suppliers (internal and external), manufacturing equipment and processes to products or services and calculates financial impact on the bottom line, can be a valuable resource. Many SMEs will not have internal specialists in supply chain or risk management so a tried and tested approach and a user friendly tool will be of particular help.

4 Quantification of Supply Chain Threats

An organisation's dependency on any one supplier will be well understood by the local supply chain or procurement manager. An organisation's dependency on an internal manufacturing site will fully appreciated by the supply chain or operations manager.

What is frequently less well understood is a company's financial exposure to that site or supplier and how to consistently quantify that exposure taking into account:

- the total value of products or services that are dependent on that location
- the amount of time that products or services will be out of the market place as

a result of losing that location for a given threat

- how downstream safety stock or alternative sources effectively mitigate that supply outage
- what the ongoing impact in loss of market share will be after the supply interruption is rectified

All of the information necessary to get that true picture of the value at risk for each location will be available within the business itself, but often from different departments: Sales and gross margin predictions will be managed by Sales and Marketing, levels of safety stocks will be determined and managed by Operations.

If some specialist help can be enlisted to track down and extract this information and a suitable tool used to process it, then an organisation will get a good picture of:

- Its key vulnerabilities across its portfolio of products, presented in order of magnitude (a hit list for action prioritisation).
- The value at risk for each location which can be used to justify taking steps to mitigate that risk.
- How to respond in a crisis, particularly if the key location is also used by the competition.

The estimation of the value and risk and the management of the accompanying data can be made easy by a tool that was designed with the pharmaceutical industry in mind, SCAIR™ (Supply Chain Analysis of Interruption Risks).

SCAIR™ is used by three out of the top ten global biopharmas and has also been used by suppliers of critical materials to the biopharma sector. In some cases the software has been used in conjunction with external project support to help the company collect and build the model to speed the process and bring a fresh look to the supply chain.

4.1 Benefits

Real benefits have been realised by companies which have undertaken the quantification of their

supply chain vulnerabilities using SCAIR™. A few examples include:

- Company A bought 125kg of a particular excipient annually. The value of the purchase was low and hence the supplier relationship was not considered critical. There was no known alternative source and no safety stock was held. However when the profit dependency of a high value product on that excipient was estimated, the cost of holding the additional safety stock versus the cost of the risk could be justified without a second thought.
- Company B was 6 months away from a major product launch. The formulation of the launch drug was complex and its novelty delivery system was dependent on a highly bespoke item of machinery (which was on an 18 month lead time). The manufacturer of the critical equipment had got into financial difficulties and looked set to go into administration. The estimation of the delay associated with re-order of the equipment and the associated loss in profits was sufficient to justify investment in the failing manufacturer to avoid insolvency.
- Company C provides a huge range of critical materials to the biotech industry. They receive substantial orders from certain customers and lots of small orders from research organisations. Prior to the supply chain risk quantification project, supplier risk mitigation activities had been mainly associated with those suppliers contributing to the large orders. The use of SCAIR™ enabled the total exposure to critical suppliers of 'small order' materials to be estimated, which was enough to convince the company that its risk mitigating activities be reprioritised.
- Company D had historically bought Business Interruption Insurance for a portfolio of sites and suppliers based on Gross Margin predictions for each location. The use of SCAIR™ enabled the

company to pin point and quantify real exposures (above an internal risk retention threshold), this resulted in an estimated 15% reduction in BI premium.

5 How to Implement SCAIR™

As far as market research reveals, SCAIR™ is unique in its ability to empower non experts in the discipline of supply chain BI calculations to do the job without needing the constant support of risk consultants.

However companies using SCAIR™ have benefited from the use of external help and discussions to set up the model, provide some familiarization support and assist the client in gathering internal data in a meaningful way. Thereafter the model can be maintained by the client company.

While not essential that a company engage external support the authors highly recommend this approach.

The authors would be delighted to discuss your needs with you.

For further information on implementing SCAIR™ visit www.supplychain-risk.com or contact one of the authors.

6 About the Authors

Dr Katherine G Reid

Dr Reid is Director of Actuact Ltd (www.actuact.com) which provides project management, internal and 2nd party audit to ISO9001:2008, business development and general management services primarily to the life science sector. She has extensive management experience including supply chain and quality having worked for over 23 years in the biopharmaceutical and health service. Dr Reid can be contacted by email at katherine@actuact.co.uk or by telephone (+44)0131 200 6302

Catherine Geyman

Catherine Geyman is a Director of Intersys Ltd, which provides IT services and specialises in supply chain risk consultancy. She is the originator of the supply chain risk quantification tool, SCAIR™ and has detailed experience of helping companies understand their supply chain risks, particularly in the pharmaceutical industry, where she has 13 years' experience. Catherine can be contacted at Catherine.Geyman@intersys.co.uk

7 Works Cited

1. **Morris, Di.** Presentation- 2008 to March 2009 and April 2009 to March 2010 Deficiency Data Review. *MHRA Website*. [Online] July 12, 2010. [Cited: December 12, 2010.]
<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/Commondeficiencies/index.htm>. N/A.
2. **FDA.** Drug Shortages- Current Drug Shortages. *FDA*. [Online] March 29, 2011. [Cited: March 30, 2011.]
<http://www.fda.gov/drugs/DrugsSafety/DrugShortages/ucm050792.htm>.
3. —. Question and Answers on the Propofol Shortage. *FDA*. [Online] [Cited: Decemeber Tuesday 14, 2010.]
<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm209227.htm>.
4. **PWC.** Supply Chain Risk Assessment, KnowledgeLine June 2009. *PWC*. [Online] [Cited: March 30, 2011.]
http://www.pwc.com/en_GX/gx/pharma-life-sciences/pdf/supply-chain-risk-assessment.pdf.
5. **Genzyme Corporation.** United States Securities and Exchange Commission Form 10K. *Genzyme Corporation*. [Online] For Fiscal Year Ending Decemeber 31, 2009. [Cited: April 4, 2011.]
http://www.genzyme.com/corp/investors/XBRL/As-Filed_2009_GENZ_Form_10-K.pdf.
6. **Johnson and Johnson.** United States Securities and Exchange Commission Form 10 K for Fiscal Year Ending December 2010. *Johnson and Johnson*. [Online] [Cited: April 4, 2011.]
<http://files.shareholder.com/downloads/JNJ/1212889274x0xS950123-11-18128/200406/filing.pdf>.
7. **PWC.** From vulnerable to valuable:how integrity can transform a supply chain -Achieving Operational Excellence Series. *PWC*. [Online] [Cited: March 30, 2011.]
http://www.pwc.com/en_US/us/supply-chain-management/assets/pwc-sci-112008.pdf.
8. **Shin Etsu Public Relations.** Shin Etsu News. *Shin Etsu Corporation*. [Online] [Cited: February 7, 2011.]
<http://www.shinetsu.co.jp/e/news/s20070906.shtml>.
9. **Covidien.** Dear Nuclear Medicine Professional, Letter, Septemeber 15,2010. *FDA*. [Online] [Cited: March 30, 2011.]
<http://www.covidien.com/imageServer.aspx?contentID=18281&contenttype=application/pdf>.
10. —. Revised November 19 ,2009 Molybdenum99 (Mo 99) shortage/Techneium (Tc 99m) Supply Frequently Asked Questions. *Covidien*. [Online] [Cited: March 30, 2011.]
<http://www.covidien.com/imageServer.aspx?contentID=16296&contenttype=application/pdf>.
11. **Shin Etsu Public Relations.** Shin Etsu News. *Shin Etsu Corporation*. [Online] [Cited: February 7, 2011.]
<http://www.shinetsu.co.jp/e/news/s20081030.shtml>.