Understanding risk in pharmaceutical supply chains

ReMediES

RE-configuring MEDIcines End-to-end Supply

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Introduction to ReMediES and supply network risk

The ReMediES (Reconfiguring Medicines End-to-end Supply) project - involving 22 industrial partners comprising global pharmaceutical companies, major contract manufacturing organisations, equipment manufacturers, and logistics specialists – examined future pharmaceutical supply chains supported by novel technology.

These technology interventions spanned the end-to-end pharmaceutical supply chain: R&D, Primary Manufacturing, Secondary Manufacturing, and Distribution to patients. The ReMediES project delivered outputs that are captured in Badman and Srai (2018) – see academic references at the end of this document.

This briefing sets out the key outputs emerging from the strand of activity linked specifically to the management of pharmaceutical supply risk.

Key Outputs

There are multiple challenges involved in the supply of pharmaceuticals. Some of these include quality and availability of key ingredients, as well as issues around the authenticity of drug products.

The safety and reliability of medicines supply is often affected by long lead times, complex global manufacturing footprints, and the challenges these presents on forecast accuracy. Supply security is further compounded by the need to comply with strict requirements in manufacturing, and regulatory scrutiny that may result in production disruptions.

Risk in this context is often associated with drug shortages: events that prevent patients getting the right medicines at the right time. In traditional supply chains, supply risk is typically managed through increased inventory. However, excessive inventory is unsustainable, and may conceal the variety of factors that may result in supply disruption.

This project therefore offers multiple lenses to focus on pharmaceutical supply chain risk:

1. Real-world data analysis to aid better prediction of disruptions and supply shortages;

2. Expert-driven risk prioritisation, to unravel complex interdependencies between potential causes of supply failure;

3. Simulation-based assessment of new manufacturing technologies to mitigate disruption and reduce inventory.

Outputs are generated at three levels, each contributing to more informed risk mitigation:

•   Industry-wide: Informing institutional action ahead of disruptive events;

•   Commercial Supply Chain: prioritising mitigation actions based on system-wide potential impacts;

•   Clinical Supply Chain: Inventory and waste reduction implications from the adoption of Just-in-time production.

Predicting Disruption Through Incident Data Analysis

In the last decade the global pharmaceutical market has faced critical shortages of certain types of drugs, reaching crisis point in 2011. The number of new drug shortages reported annually is on the rise again, prompting the study of historical datasets to identify which disruption events and supply chain characteristics are most likely to trigger shortages.

Data Gathering and Analysis
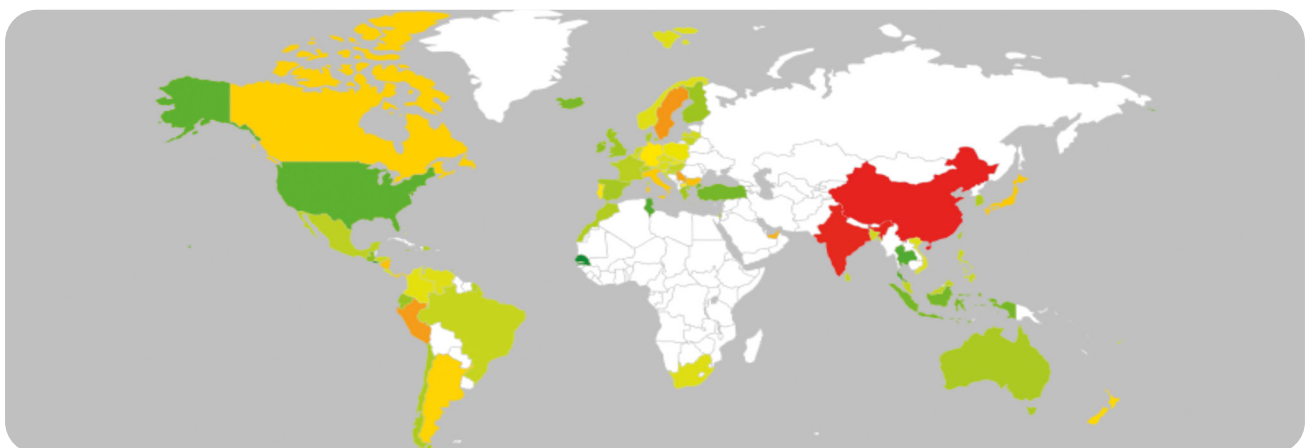
The study considered the following datasets:

- Internal company data: collected from supply chain risk experts.

- Industry wide data: Public domain data from US and EU regulators, which describe:

  - Most frequent root causes.

  - Most influential product and process characteristics.

  - Non-compliance events.

Across both internal and industry datasets, there are some attributed root causes that most frequently occur, namely demand variability and quality issues. Within quality issues, most are due to inadequate procedures, or poor adherence to them.

The analysis focussed on two industry incident datasets (US FDA Product Shortages and US Enforcement Reports) concluding that:

- Alimentary tract and Metabolism was the most frequently disrupted ATC Therapeutic Area.

- By dosage form, injectable drugs were the most troublesome across the same two datasets, reflecting the greater challenges associated with sterile manufacturing (see chart opposite).

Additional evidence from the US FDA Inspection results and EMA GMP Non-Compliance reports illustrates the influence of geographic location of facilities on poor inspection outcomes, in particular, China and India are the two countries most likely to have adverse results (see map below).

FDA Drug Inspections resulting in OAI (adverse FDA inspections) from 2008 -2017, normalised by #inspections
Colour coding represents; Order of Likelihood; ● >8%, ● 6.5-7.999%, ● 6-6.499%, ● 5-5.999%, ● <5%)

The disruption that follows an adverse inspection outcome should not be underestimated. Disruptions are often significant as companies attempt to resolve issues, in order to avoid the ultimate sanction of regulatory shutdown.

Beyond the contextual factors outlined above, analysis of events preceding drug shortages yielded further insights on the operational triggers contributing to drug shortages. These triggers are set out on the next page.
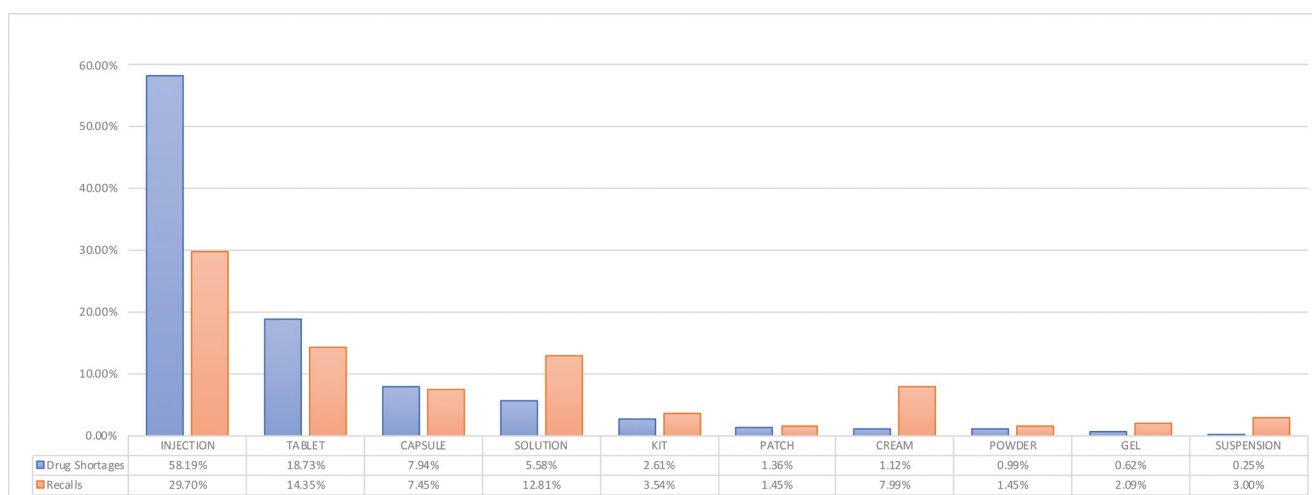
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Key Triggers for Drug Shortages

For drugs reported as in shortage or discontinued by the FDA as of August 2018, further analysis identified linkages to preceding interruption events impacting the relevant companies.

Events such as Warning Letters, Recalls, Import Alerts, Certificate Withdrawals and adverse Inspection Results were considered, up to 4 years prior to the interruption. This represents an upper bound on the time it takes to impact the market (due to long cycle times, lengthy remediation plans and significant safety stock holdings).

The most frequent 'triggering event' was an adverse FDA inspection (OAI) which preceded 69% of individual shortages; 73% if Product Discontinuations are excluded. This result reflects company responses to an adverse inspection result: typically, a company will initiate remediation works which will at worst interrupt production over months/years, or at best, divert scarce resources from normal production activities, potentially impacting quality.

% of FDA Drug Shortages & FDA Enforcement Reports (Recalls) by Dosage Form (Top 10)

	INJECTION	TABLET	CAPSULE	SOLUTION	KIT	PATCH	CREAM	POWDER	GEL	SUSPENSION
Drug Shortages	58.19%	18.73%	7.94%	5.58%	2.61%	1.36%	1.12%	0.99%	0.62%	0.25%
Recalls	29.70%	14.35%	7.45%	12.81%	3.54%	1.45%	7.99%	1.45%	2.09%	3.00%

Courtesy of Intersys

Of the 33 parent companies reporting shortages, 19 experienced major network interruptions which resulted in manufacturing stoppages or prolonged slowdowns. Downtime at each impacted plant often triggered multiple drug shortages.

Product discontinuations also appear to be influenced by drug pricing. Many 'hard to make', sterile generics have low, set prices. With increasing costs and relatively low margins in the generics sector, license holders often withdraw from the market, increasing the fragility of the supply base.

In conclusion: drug supply disruptions are triggered by a wide variety of complex, often interdependent events. However, if a company that manufactures injectable drugs in an already constrained marketplace, receives an adverse inspection report, then that manufacturer should be flagged as 'at risk' and shortages could be expected to follow.

These insights have been used to support risk categorisation and consolidation, with an updated risk assessment tool for incident monitoring being developed through Intersys (available at https://supplychain-risk.com/regulatory-incident-monitor)

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Identifying Risk Interdependencies

Defining a sector-wide pharmaceutical supply chain risk classification

This activity sought to categorise and prioritise a generic set of risks within pharmaceutical supply chains, and then to understand possible interdependencies between them. The proposed approach is described in details in Settanni et al (2018) – see academic references at the end of this document

Risk assessment within the industry typically focuses on a specific event within a complex manufacturing supply chain. However, mitigation strategies should consider multiple events that, in combination, may result in significant supply failures. These interdependencies may be difficult to quantify, and are rarely considered by risk professionals.
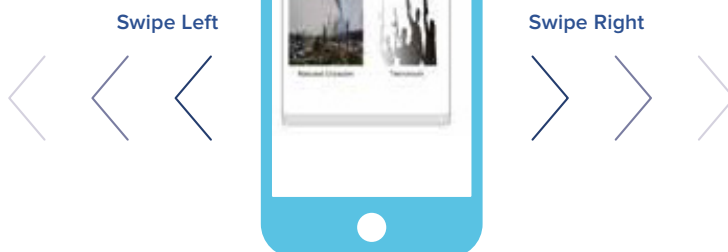
One of the outputs of this activity was an agreed, sector-wide view on risk in pharmaceutical supply chains. Risks were identified through extensive industry-academic workshop discussions, leading to the identification of an initial set of 121 risks through the supply chain. These were grouped according to 27 root causes.

The chosen experts represented a typical end-to-end pharmaceutical supply chain, coming from businesses involved in primary and secondary manufacturing, distribution and retail pharmacy, as well as risk consultancy.

Understanding interdependencies between risks: A Gamification approach

The direct influence of each risk item on any other item is related

Swipe Left

Swipe Right

A mobile application designed to elicit knowledge from risk management experts
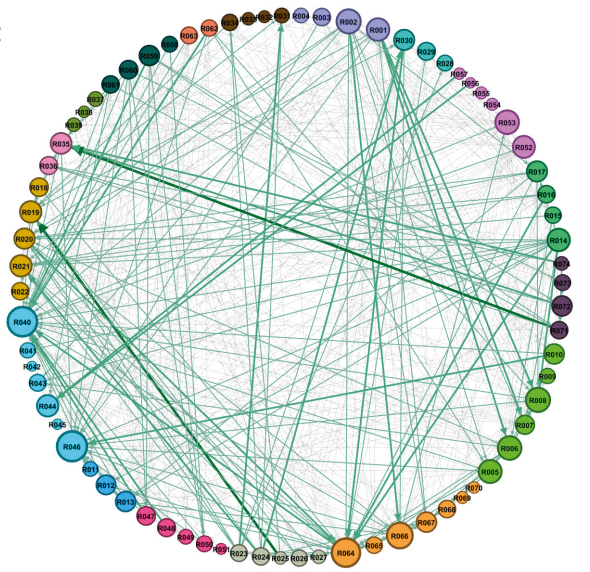
In a follow-up step, supply chain risk experts were asked to identify which risks may influence other risks, and what is the magnitude of such linkages. Addressing these questions gave a deep understanding of possible interactions between risk events.

To facilitate a user-friendly interrogation of risk interdependencies, a gamification app (pictured left) was developed so that risk experts could evaluate the potential 539 links arising from the 74 risks items identified.
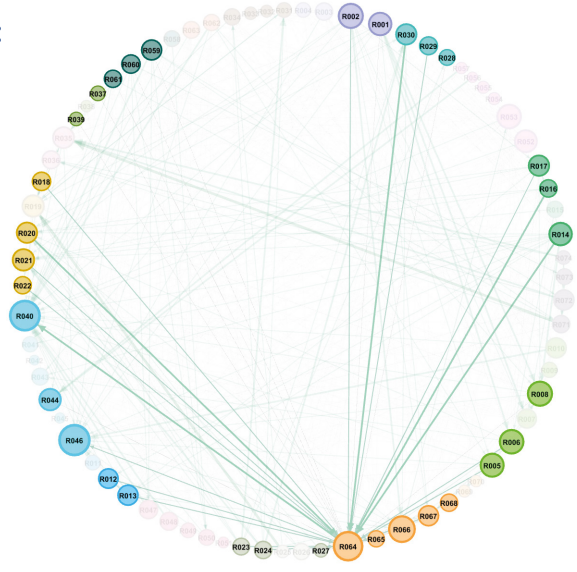
Expert engagement through the gamification app for the assessment of risk interdependencies produced a network visualisation of risk interdependencies (picture overleaf), and the associated network analytics.

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Risk network visualisation: a) overall interdependencies between risks (the stronger the relationship, the darker the arc); b) Detail on sub-network centred on a specific risks
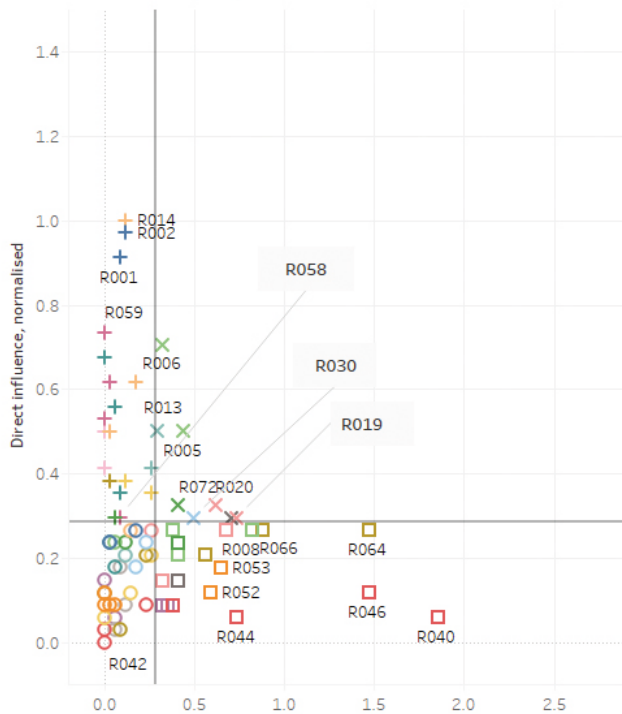
A:

B:

The interactive visualisation tool allowed the experts to further examine specific risks of interest and highlight those most directly linked to them. Analytics were deployed to compute how risk propagates throughout the network, as any risks may in depend, or exert an influence on any other.

The analysis yielded a concise "two-by-two" categorisation of the 74 risks (graphically plotted below):

I. Upper-Left: Influential risks.

II. Upper-Right: Unstable risks, both influential and dependent.

III. Lower-Right: Dependent risks.

IV. Lower-Left: Mostly autonomous risks.

Risks categorisation plots. Those included in the upper-right quadrant can be unstable and difficult to predict, whilst risks in the bottom-left and can be safely discarded

Evaluating risks and benefits in Just-In-Time clinical supply

Inventory in pharmaceutical supply chains

Conflicting objectives are not uncommon in managing inventories in pharmaceutical supply chains: excess stock could improve service; however holding inventory is costly, and may eventually result in write-offs and disposal of unused medicines.

Project ReMediES has explored a range of manufacturing technologies targeting inventory reduction whilst improving service to patients.

Within the risk strand, activities were carried out to examine trade-offs between service improvement and holding inventory. A case study in Clinical Trial Supply Chain (CTSC) delivering investigation medicinal products was considered to test different replenishment models. These challenges are of course not unique to the CTSC, and can apply to future commercial supply chains, particularly due to increased personalisation; more responsive supply requirements; and potentially more distributed manufacturing footprints.

Unlike the analyses presented in the previous section, looking at inventory dynamics required more detailed, quantitative data. Technical details are provided in Settanni and Srai (2018) – see academic references at the end of this document.

The "JIT pharmacy" concept

A commonly held view is that high availability in multiple locations globally is only achieved at the expense of efficiency. In current CTSC settings, it is not uncommon that less than half of manufactured investigational medicine products are likely to be used by clinics.

This provides a strong motivation for exploring automation and industrial digitalisation technologies. An innovative 'just-in-time' pharmacy concept was tested in a simulation environment, comparing the performance of a hypothetical CTSC that featured this technology intervention, to that of a conventional CTSC. The introduction of just-in-time principles, enabled by new manufacturing technologies, challenges commonly held views on the relationship between holding inventory, and attaining high service levels.

In particular, expected performance levels in terms of inventory emerge from dynamic interaction between the demand and supply based factors over time. The following factors were included:

- **Geographically dispersed demand signals:**
    - How the clinical study design develops,
    - Recurrence of clinic visits,
    - Quantity of medicine dispersed.

- **Manufacturing capabilities:**
    - Cycle times,
    - Inspection outcomes,
    - Replenishment/reorder policies.

Simulating with different assumptions on inventory stock levels and logistics policies provides sensitivity analysis and revised policy holding strategies at the various stock holding points. JIT technology interventions, demonstrated potential to produce stock near on-demand, with potential reductions in unused inventory of between 67% to over 80% in the particular case considered here.

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Concluding remarks on pharmaceutical supply chain risk

The work led by the Centre for International Manufacturing in collaboration with Intersys and other industry partners, provides a multi-disciplinary view on the nature of risk in pharmaceutical supply chains: from the statistical analysis of supply disruption events, to risk interdependencies across the end-to-end supply chain, through to the evaluation of new technology interventions in terms of inventory, waste and service levels.

Analysing mitigation strategies is crucial to inform supplier selection, order allocation, facility locations, inventory levels and overall coordination across the supply chain. Insights from this research will inform future supply chain resilience strategies in medicines manufacturing.

Unlike previous research, pharmaceutical supply chain risk was approached from multiple levels of analysis – macro (whole sector), meso (individual supply chains), and micro (unit operations technology. Risks were not considered in isolation, rather, they were characterised and prioritised based on possible interrelationships between them. Supply network design tools were deployed to evaluate novel technology interventions that challenge commonplace trade-offs between economic efficiency and medicines overage in CTSC, as well as future commercial supply chains.

As with other strands within ReMediES, this activity has benefited from successful pre-competitive collaboration between industry and academia. Building on unprecedented engagement with supply chain risk experts, and "real-world" data, this research contributes to making an impact on industry practice, by providing novel approaches and tools to support pharmaceutical supply chain risk analysis.

Centre for International Manufacturing (CIM)
CIM is a research centre at the Institute for Manufacturing focusing on strategic and operations management research in close collaboration with industrial partners. The Centre has developed a strong industrial–policymaking–academic community and provides expertise and support in the area of international manufacturing and global value networks, with particular focus on capability development and strategic network design. It provides briefings on globalisation and international manufacturing for industry and government.

Institute for Manufacturing (IfM)
The IfM is part of the University of Cambridge's Department of Engineering. It brings together expertise in management, technology and policy to address the full spectrum of issues which can help industry and governments create sustainable economic growth.

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