HUMAN FACTORS: THE PHARMACEUTICAL SUPPLY CHAIN AS A COMPLEX SOCIOTECHNICAL SYSTEM

Running title: Sociotechnical supply chain issues

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Abstract

Background: The Covid 19 pandemic has exacerbated pre-existing weaknesses in the global supply chain. Regional assessments by the Food and Drug Administration (FDA), European Medicine Agency (EMA), and independent consultants, have demonstrated various contributory causal factors requiring changes in policy, relationships, and incentives within the dynamic and developing networks. Human Factors/Ergonomics (HFE) is an approach that encourages sociotechnical systems thinking to optimise the performance of systems that involve human activity. The global supply chain can be considered such a system. However, it has neither been systematically examined from this perspective.

Methods: In 2015, the UK Chartered Institute of Ergonomics and Human Factors established the Pharmaceutical Sector Group. This unique group is open to all who work in the pharmaceutical sector at any level and in any discipline who share the vision of a pharmaceutical system that places an understanding of HFE at the heart of improving the use of healthcare products throughout their life cycles including their supply chains.

Results: For this complex system to work efficiently it is paramount that we have effective coordination and integration between the different elements in the supply chain. HFE can give valuable insights and solutions for developing these complex social-technical systems effectively.

Conclusion: By partnering with international groups such as Biophorum and Bio Supply Chain Management Alliance, the wish stimulate discussion about how sociotechnical thinking about HFE may help develop better monitoring and investigative techniques to strengthen global supply chains.

Introduction

The current Covid 19 pandemic has pushed the importance of the supply chain to the top of the political agenda in many countries. A growing number of hospitals both in the US and EU are reporting shortages of medicines needed to treat patients with COVID-19[1-3]. Stocks of important products including opiates, propofol, midazolam and others have frequently been at risk, if not out and regulatory lead times are an issue to find alternate sources of the same product or register new ones. The active pharmaceutical ingredients often come from China and India and many months may be needed for manufactures to scale up and obtain authorization before being added into the final product in Europe.

How have regulators responded in the EU and US?

What do the regulations say to address the supply chain? Internationally, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12 are the agreed guidelines for the quality system for the 'company' (marketing authorisation holder and manufacturing sites) that includes the supply chain. The guidelines recognise that *'Supply chains involve multiple stakeholders (e.g. marketing authorisation holders (MAHs), research organisations, manufacturers, Contract Manufacturing Organisations, suppliers)'*[4]. The guidelines state that it is important that these stakeholders *'interact to effectively utilise knowledge and manage changes during the product lifecycle'* and that '*a company has to manage communication of information and interactions of pharmaceutical quality systems across multiple entities (internal and external)'*[4]. The emphasis in these guidelines is on documentation which describe 'communication mechanisms' without further details about how MAHs can achieve these. The Food and Drug Administration (FDA) had already noted in their assessment of the supply chain that such guidelines do not include '*more advanced levels of quality management, which aim to robustly detect vulnerabilities and address them to prevent occurrence of problems, as well as establishing a culture that rewards process and system* improvements'[5]. These regulations also do not go very far in prescribing solutions which

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are left to the discretion of pharmaceutical regulatory bodies who may not have the necessary skills or structures to solve shortages. What we should focus on is the resilience of supply chains that is related to HFE and how it applies to all involved in the supply chain.

To define HFE we refer to the International Ergonomics Association (IEA) definition as '*the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data, and methods to design in order to optimize human well-being and overall system performance'*[6]. A resilient system able to anticipate, monitor, learn and adapt so it can sustain functioning despite disruptions which is based on an understanding of HFE. How HFE has been considered in supply chain design is the focus of our discussion.

In July 2020, the European Commission raised concerns about increasing number of reports of shortages affecting all EU Member States[7]. As a result, the Commission will be launching a study to provide data on the causes of medicines shortages and identify possible further actions to further address this risk. The aims are to enhance oversight of global manufacturing and clarify responsibilities to ensure quality of medicines. This is not the first time such an analysis has taken place as the Covid-19 pandemic has aggravated a pre-existing problem. Between 2012-2016 a marked increase in drug shortages in the US was observed. In response, in 2019 the US FDA assessed what were the causal factors underlying these shortages and concluded there was 'no simple solution'[5]. They identified three main broad causal categories involving economic factors that drive both public and private sector decision-making:

1. Lack of incentives to produce less profitable drugs. We recognise this as a significant challenge for older products that have gone generic, but with price levels so low there is no incentive to produce.

2. The market does not recognize and reward manufacturers for mature quality management systems.

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3. Logistical and regulatory challenges make it difficult for the market to recover after a disruption.

In addition, the FDA noted the need for more comprehensive and reliable information about the effect of shortages. They alluded to product-specific information being tightly guarded as trade secrets and commercially confidential with 'limited' public information assessing maturity of quality management systems. However, what is notable is that there is no mention of sociotechnical concepts about resilience or HFE in determining supply chain quality.

In 2012, the European Medicines Agency (EMA) reviewed supply shortages and concluded the industry had a 'very reactive' approach to risk management while acknowledging that the causes of shortages were 'varied and complex' with the main challenge being about how to assess and develop risk minimisation activities .For example, what can we learn from the insurance industry who use analytic tools[8]? An expert report by Birgli AG (2013) pointed out that, although individual countries have reporting mechanisms of varying degrees of effectiveness about shortages, there is no centralised oversight or coordination between regulatory or other health agencies and other stakeholders[9]. To this effect EMA has put into place a "Shortages Catalogue" which is very limited when compared to the national registers which are also listed[9].

Although regulatory agencies and numerous other groups have discussed many individual aspects of shortages, few have looked at the topic holistically as a systems issue. Economic factors are important system drivers such as delays in payment, tendering, especially generics and parallel distribution. However, their contribution to shortages is nuanced and varies over time. It is evident that active oversight and active mitigation action is not present centrally (perhaps as it should be) with varying degrees of oversight and mitigation activity country by country. Mitigation seems to be largely limited to blocking parallel exports rather than active measures based on leading indicators.

What do we know about the global supply chain pre-pandemic?

The European Parliament produced a report in April 2020 summarising global actions[3]. To illustrate the global nature of this challenge, a study of 28 European and Asian countries in 2018 illustrated how drug shortages emerged as a problem regardless of their geographical location, level of economic development, or type of health care system[11]. Despite being so common, drug shortages are rarely defined in a precise and aligned way within/across the studied countries' legislation; often shortages were defined indirectly or not defined at all.

Currently, drug shortages can be expressed in four different ways, according to whether they affect either the demand or supply side, and the way they impact either drug delivery or availability to patients. This means the way drug shortages are defined depends very much on a stakeholder's position within the supply chain. Lack of any definition adopted within a national health care system, as well as diversity of definitions in the same system, or incomparability and inconsistency of definitions across systems or countries, can negatively affect reporting, communication, and comparative analyses of the problem of drug shortages, including their scale and effects. The disparate (national) organizations responsible for gathering information on drug shortages in the same country may lead to a multiplication of efforts or confusion in interpreting the results of analyses, especially when different methodologies for gathering information are used. The public service obligation imposed on suppliers of medicines, that can be important in securing appropriate access to drugs, are often limited to reimbursed medicines only and were difficult to execute in practice in the studied countries[11].

What progress has been made with industry initiatives to improve the supply chain?

As an example of an industry initiative by manufacturers, Biophorum coordinated unique global collaboration of 53 manufacturers and suppliers with multiple working groups tackling different

topics one of which was entitled Supply Partner Forecasting and Demand Planning (FDP) and Supply Chain Mapping workstreams[12,12]. These Biophorum groups have produced a best practice forecasting and supply planning guide for the biopharmaceutical supply industry and assessment tool. This guide defines the participating biomanufacturers' and suppliers' perspectives of the industry's current roadblocks, the best practices that need to be more widely adopted and the business case for change. In addition, A draft best practice guide to Risk Management in the Biologics Supply Chain is expected in 2020.

However, we were particularly interested in the output from the separate Human Performance working group as this relevant to all pharmaceutical processes including the supply chain. This consensus report was the first of its kind for the pharmaceutical sector and so sets a landmark in sociotechnical thinking for pharmaceuticals[14]. The group recognised the inadequacy of blaming human error as a root cause and that current investigative approaches were ineffective at reducing repeat events. This group concluded that complex socio-technical realities of current pharmaceutical operations, such as the supply chain, demand change. They recommended adoption of a better understanding about how and why things go wrong in the first place comparing the difference between work-as-imagined versus work-as-done. They produced a report about how to integrate HFE thinking into design of work and its execution, conduct work observation, enable open reporting, and focus on organisational learning. Some of the main solutions the report recommended include:

- Using a wider range of systems methods and techniques to understand factors and causes underlying deviations

- Learning from workers through conversation and observing work to identify conditions that challenge successful execution

- Recognising the value of low-technology job aids closer to a task

- Developing and evaluating metrics which encourage positive capabilities and behaviours to supplement the traditional metrics of deviations.

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The Bio Supply Chain Management Alliance (BSMA) is an independent membership-based organisation comprised of hundreds of companies active along the supply chain – from sourcing, manufacturing to distribution and logistics. They have put in place global working groups and sessions to tackle global issues in supply chain while addressing local problems. Online seminars, taskforces and teams are addressing short term challenges while planning for how we can learn for the mid and long-term.

From these reports and industry initiatives what we can conclude and what has the Covid 19 crisis shown us?

We have focussed this assessment primarily of the pharmaceutical supply chain although many factors can be extrapolated to other healthcare products. It is apparent from the reviews performed by the major regulatory agencies that HFE have not been addressed directly. However indirectly, HFE are implicit by the recognition of the importance of factors such as incentives and cooperation. There are many organisational factors that have been identified such as conflicts between price and risk mitigation, sourcing dependency on one or two countries such as China and India, air freight capacity and lack of coordination between different regulators and government agencies. The supply chain issues caused by COVID-19 have been split into four main categories:

1. personal protective equipment,

2. medical products,

3. diagnostics.

4. other medical devices.

HFE links all these together as part of understanding and designing a complex sociotechnical system such as the pharmaceutical supply chain. HFE is important at all levels of a complex system: the individual, the team, organisation, regulator, national and international interactions. Economic and regulatory policy measures are important system drivers such as potentially re-issuing temporary "exclusivities" to motivate companies to produce products that are going off production or where

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production is restricted down to one or two global sites. Taking regional approaches without recognising the true extent of the supply chain from patient to the factory globally may lead to the illusion that systems approach has been taken. Because of conflicting objectives as revealed in the reports from FDA and EMA, we need the overarching objective of all supply chain stakeholders to ensure patients get the right medicine, at the right time in the right place.

Trust and confidence are critical components because they set the foundation and tone of all partnership so that more reliable forecasting, such as developed by Biophorum, provides key signals that biomanufacturers can provide to their suppliers. We welcome the EMA guidance on detection and notification of shortages with its recommendations about common definitions of drug shortage and what data should be reported[15]. Centralised reporting is needed as part of a broader quality system built on vigilance including measure process performance and prioritisation around essential medicines. The interconnectedness of systems with common features are based on HFE which should be part of the future basis for collaboration between all stakeholders involved in supplying health care products.

Conclusion: Future Actions

Within the UK, the Chartered Institute of Ergonomics and Human Factors (CIEHF) has established a unique Pharmaceutical sector group to provide a means of consolidating knowledge around pharmaceutical HFE, foster new insights, and support the need for models of HFE integration and competency development across the sector from bench to factory to patient. We recommend in future systems professionals who are competent in HFE can input into demonstrating how the supply chain can benefit from a HFE approach.

This CIEHF group will liaise with supply chain professionals, within organisations such as the BSMA to establish human performance standards within the pharmaceutical supply chain, developing corresponding metrics building on the work already performed by the groups in Biophorum and BSMA. The CIEHF Pharma group welcomes members from any part of the healthcare product supply

chain

(https://www.ergonomics.org.uk/Public/Get_Involved/Sector_Groups_SIGs/Pharma_Human_Factor
s/Public/Get_Involved/Group_Details/Pharma_Human_Factors.aspx?hkey=fd20a5a5-714d-4d8c-
b060-f00f50835f46). With the EU Commission performing a further study about shortages of
medicines, it is time to put HFE at the centre of any strategy.

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