

The response of the Irish pharmaceutical manufacturing sector to the COVID-19 pandemic with a focus on Lean and JIT

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Abstract

Background: Just in Time (JIT) and Lean manufacturing are concepts that originated in the automotive industry and were then adopted by pharmaceutical and biopharmaceutical companies during the 1990s. However, the Covid-19 pandemic and the urgent demand for pharmaceutical treatment challenged JIT and Lean manufacturing processes. Production of Covid-19-related medicines increased, putting pressure on global supply chains and operations. This also hindered the production of medicines using the same or similar materials. Thus, questions are raised concerning JIT and Lean supply chains in the pharmaceutical industry.

Objectives: The present study aimed to explore (1) if material and supply constraints occurred due to the Covid-19 pandemic, (2) how companies were impacted and managed and (3) if changes are required to future proof the JIT supply chain approach for future global events.

Design: A mixed-method cross-sectional survey design was used and focused on material supply, qualification and validation in Irish pharmaceutical manufacturing sites.

Methods: Employees working in the Irish pharmaceutical manufacturing industry were recruited using convenience sampling through online advertisement using the social media platform 'LinkedIn'. Quantitative data was analysed using percentages and qualitative data from free-text responses were used to add context to the quantitative survey questions.

Results: A total of 41 participants were recruited. The results suggested that the pandemic had a negative effect on material availability according to 81% of participants. This translated to delays or stoppage of production activity and was mainly handled by sourcing new materials (70%). To cope with future global crises, 60% of participants recommended more flexibility in future validation processes while 78% of participants acknowledged the importance of validating additional suppliers. A hybrid model of manufacturing and supply chain management was also a preferred approach to exclusive Lean and JIT (42%).

Conclusions: The production of non-Covid-19 medicines was adversely affected by the Covid-19 pandemic, but the pharmaceutical industry in Ireland demonstrated resilience and collaboration in response to these challenges. This study suggests that the JIT and Lean manufacturing model should be adjusted to ensure medicine supply chains are not disrupted during future global events.

Keywords

Irish pharmaceutical industry, manufacturing, COVID-19, Lean, Just in Time (JIT), resilience, collaboration

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Introduction

JIT and Lean manufacturing

Early innovations of efficient manufacturing production operations have origins in the motor and textile industries.¹ At the start of the 20th century, the Toyota Motor Company pioneered the Toyota Production System (TPS),² a Lean method illustrated as the TPS house, which depicts the foundation, pillars and goals of the model (Figure 1). The two main pillars of the TPS system are Jidoka and Just in Time (JIT). Particularly, Jidoka is a process where an operation stops automatically upon defect detection, and JIT is a concept that offers efficiencies by minimising the raw material input and excess outputs of a process. JIT offers waste reduction, space saving in warehouses, low excess stock levels that can depreciate, and maximises the potential for reduced costs and increased profit if executed and maintained correctly. The efficiencies offered by the Lean model were obvious as Lean production focused on all aspects of waste, over-production, over-processing, errors, equipment reliability and inventory levels. This offered an insight into how agile working could benefit the western style model of mass production. Books like ‘The Machine that changed the World’³ brought these TPS production innovations to a mass audience that adopted its philosophy into their organisation. Lean manufacturing became a global phenomenon, transforming the process from a mass production mentality to a ‘consumer demand driven’ and ‘focus on efficiency’ model.

The global pharmaceutical industry, biopharmaceutical industry and MedTech industry are no different to most globalised industries. Supply chains are large, complicated, multi-layered and interdependent on each other. It is in essence an ecosystem of business partnerships, forged by a demand for materials which will ultimately support and produce medicines that are essential for both individuals and healthcare systems.⁵ Although the pharmaceutical industry is not the first industry to have taken Lean manufacturing on board, the switch to the cost-saving principles of this philosophy has gathered momentum since the turn of the 21st century.⁶ The emergence of a more competitive marketplace, the loss of patents on blockbuster sales products and the desire to maximise profit⁶ increased created pressures on the pharmaceutical industries that have encouraged change. This environment highlighted the value of new innovation which in turn led to increased pressure for the pharmaceutical industry to adapt and become leaner and more innovative.⁷ More and more drug companies are seeing the benefits of adapting to such a model.⁶ More specifically, Lean Six Sigma methodologies that are in line with Operational Excellence have been found to be a beneficial and effective toolset for

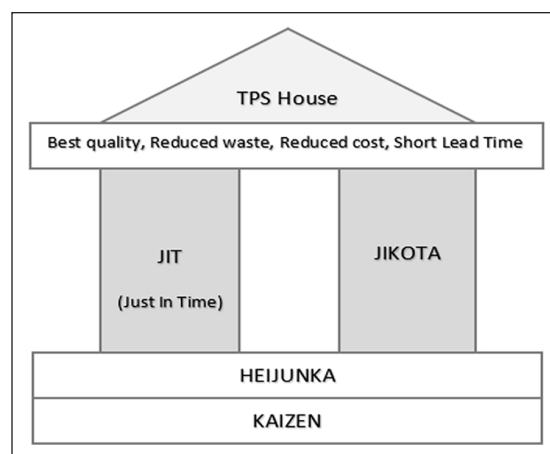


Figure 1. TPS house.⁴

problem resolution and process enhancement in pharmaceutical manufacturing facilities.⁷

Complexity. Research in the pharmaceutical industry shows a mixed picture of how successful adopting JIT manufacturing and Lean principles has been. It has shown that the benefits of Lean are several,⁷⁻¹⁰ including its compliance with current Good Manufacturing Practices (cGMP).⁸ Yet, there is also evidence of several pitfalls.¹¹ Geller⁶ suggests that the value of JIT is observed in companies with low complexity and low variability, which aligns with its success in the automotive industry. Yet, pharmaceutical production processes, characterised by high complexity and high variability, mean it is harder to implement Lean. Particularly, large companies find easier paths to Lean manufacturing based on scale of operation, while smaller companies find it more challenging.¹²

Regulation. There is added complexity to Lean implementation in highly regulated environments such as the pharmaceutical industry, as any changes to practice must also adhere to national or international regulation.¹¹ Change can often be considered cumbersome, as the rewards can be outweighed by the effort.¹³ Indeed, regulation is demonstrated as a major factor in the decision to implement Lean with some researchers seeing an uneven fit between the two, and regulation as a barrier to implementation of Lean,^{11,14} while others see the two as a natural fit, because if a process can be simplified and made more efficient then it is easier to understand and thus regulate.^{9,15}

Supply chain predictability. Managing market demand and supply chains is also challenging. It is noted that predicting market demand can present difficulty, especially since pharmaceutical manufacturers are known to sell to wholesalers and not directly to the customer, which places them

one step away from accurately measuring the market demand.¹⁴ Wang and Jie¹⁶ and Bastani et al.¹⁷ focus on supply chain uncertainty in the industry, acknowledging that a supply chain can also come under pressure from disasters like an earthquake, a tsunami or a hurricane. The ripple effects of such events can cause major supply chain disruption, due to the interlinking nature of the supply network. Delays at one supplier can lead to a knock-on delay at the next site and so on.

The COVID-19 pandemic and supply chains. Exposure to major global events like the Covid-19 pandemic provides a challenge to the successful operation of Lean and JIT manufacturing systems.¹⁸ Evidence of this impact was made prominent over recent years of production (2021–2022) as global supply chains were squeezed to the point where some companies have had difficulty making product and others have had to stop or pause manufacturing. At the same time, the continuous monitoring of drug shortages as part of ongoing maintenance of healthcare systems during the Covid-19 pandemic became a critical task.¹⁹ Regulatory agencies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) expected and observed supply chain disruption, which caused lack of availability to consumers.

Early-stage development and manufacturing of Covid-19 vaccines and treatments for the global pandemic was initiated in early 2020. An initial unprecedented level of scientific sharing of data on the virus ensued its genetic makeup, characteristics and traits as a disease were shared.²⁰ These early studies suggested that medicines that were known to be effective against respiratory illnesses and infections could have an impact on Covid-19 disease progression. Thus, demand grew for non-Covid-specific anti-inflammatory treatments.²¹ Moreover, as the race to develop a vaccine candidate for the virus intensified, access to the type of equipment needed in modern biopharmaceutical production processes grew. Single-use plastic products and bioreactors, filtration devices and raw materials needed in these processes grew scarce.²²

The issue of supply chain disruption has multiple root causes, and it is difficult to pinpoint a single definitive one. The logic of JIT manufacturing relies on prediction and planning, which in turn relies on a predictable system. When an event like the Covid-19 pandemic disrupts normal supply chain patterns, it is harder to predict and plan. Therefore, we propose the examination of the elements of the systems that create unpredictability. Taking a closer look into some of these causes, we can build a picture of how the pharmaceutical industry is set up to deal with pandemic-like crises and hopefully theoretically protect pharmaceutical supply chains against such events.

Research gaps and study motivation. The literature review shows conflicting views on the suitability of Lean and JIT approaches for the complex and highly regulated pharmaceutical manufacturing sector; yet, these approaches have been incorporated in pharmaceutical production. It would be interesting to review the potential benefits and/or challenges of such approaches in a time of global crisis (Covid-19 pandemic) that shook the status quo of pharmaceutical manufacturing and added further to existing complexity and regulations. The proposed supply chain predictability challenges in times of disaster make this attempt even more significant, in preparation for future turbulences.

Aims and objectives. The aim of the present study is to assess the impact of the COVID-19 pandemic on the Irish Pharmaceutical Manufacturing Sector. The study's objectives are to explore the material availability during the pandemic and its effect on the non-Covid-19 medicine supply chain. Also, it aims to explore how companies managed and recovered from the crisis with a focus on the Lean and JIT framework. Finally, it aims to explore if current processes can be improved in preparation for future global events, focusing on the areas of material supply, qualification and validation.

Research Question: What was the impact of the COVID-19 Pandemic on the Irish Pharmaceutical Manufacturing Sector and the non-Covid-19 medicine supply chain from the lens of JIT and Lean manufacturing?

Methods

Design

The present study adopted a cross-sectional design using an anonymous online survey administered to the pharmaceutical ecosystem, in Ireland. The survey was based on existing survey methodology theory.^{23,24} The questionnaire approach was used to increase reach to a small and difficult to access population of study participants.

Participants

Participants were highly skilled professional adults working in Irish pharmaceutical manufacturing sites.

Recruitment. The study used convenience sampling for participant recruitment and followed the social media recruitment approach used by Middleton et al.²⁵ and Stoke et al.²⁶ Social media platforms allow rapid recruitment with minimal financial resources and promote snowballing. Convenience sampling also benefits the exploration of

emerging research areas where there is little or no existing literature, while promoting engagement.

Response rate. Due to the voluntary nature of the survey, and the online audience, a response rate cannot be calculated. In the case of the present study, the ease of access to a wide spectrum of hard-to-reach candidates from the pharmaceutical industry was argued to outweigh the inability to calculate a response rate.

Materials

Google forms were used to administer the online survey encompassing 16 questions to the target audience, with an option for further clarification or discussion after each of the core questions. The final two questions of the survey were free-text response options (see Appendix 1 for survey questions).

Common method bias

Participants were given a detailed information sheet with the aims of the study and how their data will be used to motivate them for more accurate responses. Also, the questionnaire was relatively short with no repeated measure to increase engagement with the survey. Scale items were phrased in a straightforward and clear way to avoid ambiguity and an option for free-text complementary answer was provided. Finally, the survey incorporated items with various scale properties (e.g. strongly agree–strongly disagree, strong positive effect–strong negative effect, multiple answer questions, free-text answer questions). These measures were taken to counteract common method bias that can be present in studies with survey designs.²⁷

Procedure

Data collection took place in autumn 2022. Participants received an information leaflet and invitation letter which outlined the study and the aim of the survey (see Appendix 3 for leaflet and invitation letter). Survey completion was estimated to take 15 min and was active for 2 months. The virtual data was stored in the Google Forms interface prior to data entry and then exported onto a password-protected Excel file on a secure network.

Analysis

Question by question analysis was performed using Microsoft Excel. Each quantitative question was analysed, and percentages were produced. Free-text responses were thematically analysed and reported alongside the trends

from the quantitative questions to add further context to our findings.

Ethics

The study received full ethical approval from the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee, Trinity College Dublin (Application number 2022-06-01). Prior to the data collection process, a Participation Information Sheet and a consent form (Appendix 3) were built into the online survey as links and informed participants about their rights and the full oversight of the study. Participants were informed that their participation was voluntary and that answers would be anonymous. It was anticipated that no participant was at risk of physical or psychological damage as a result of the study, and no deception was present.

Results

Participant and organisational background

A total of 41 participants from mostly Irish Pharmaceutical Manufacturing sites responded to the survey. The initial four survey questions were aimed to establish the participant and organisational background (Figures 2–5).

Geographically, the Leinster region provided the largest sample set. This is expected as the Leinster region accounts for majority of the Irish population. This is additionally offset by the variation seen in the category of ‘product produced at the facilities’ where respondents originated and with good variation of the types of substances produced and evenly spread. The majority (66%) (Figure 5) of facilities were also confirmed as producing either non-Covid-19-related medicines or both Covid-19 and non-Covid-19 products. The quality area featured strongly with 63% (Figure 3) of respondents being from a quality background, but good representation from other areas of the pharmaceutical industry were also observed. The sample set provides a suitable sample for the purposes of this study, which aims to assess the impact of the Covid-19 pandemic on pharmaceutical supply chains and the production of non-Covid-19-specific medicines, with a focus on Ireland.

Manufacturing and Covid-19 impact

The next series of survey questions aimed to understand to what extent the pharmaceutical industry has been impacted by the pandemic. Questions were asked to explore how the pandemic has impacted production output, if the pandemic has led to a need to source new materials, or to a change in the way organisations source new materials or validate sourcing approaches (Figure 6).

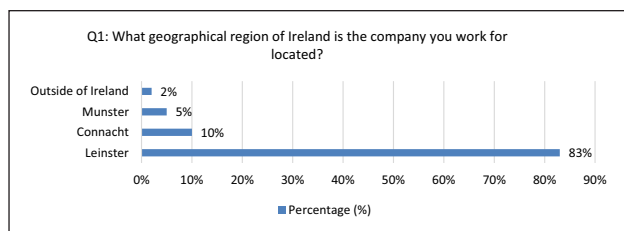


Figure 2. Study participant and organisational characteristics: question 1.

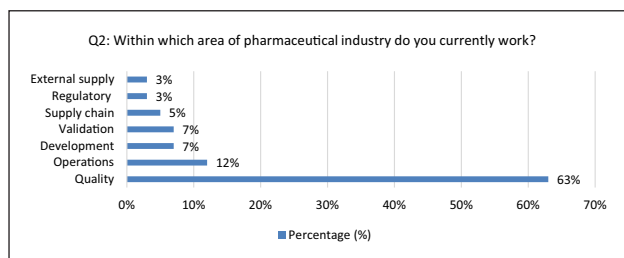


Figure 3. Study participant and organisational characteristics: question 2.

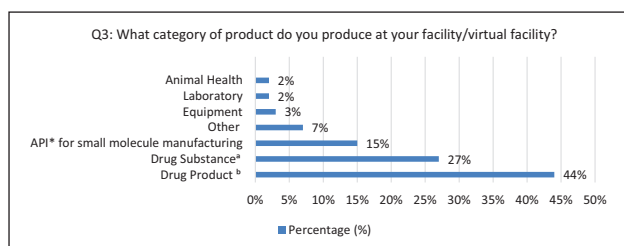


Figure 4. Study participant and organisational characteristics: question 3.

API: active pharmaceutical ingredient.

^aDrug substance (biologics or small molecule).

^bDrug product (for biologics manufacturing).

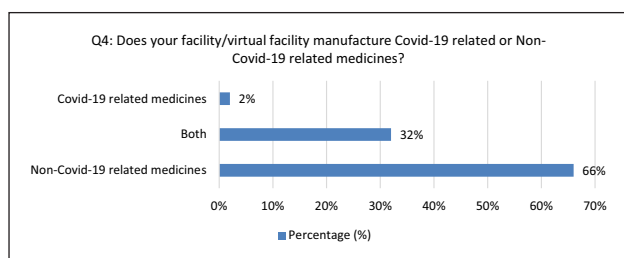


Figure 5. Study participant and organisational characteristics: question 4.

For questions Q5–Q10 in Figure 6, a clear trend emerges regarding the impact of the pandemic for the survey participants. There has been a negative effect in terms of material availability during the Covid-19

pandemic, with 81% (Figure 6, Q5) of the participants noting either a moderate or strong negative effect. This was supported by some qualitative quotes from participants also:

“Caused a hard stop in facility for 6 months due to component shortage” (Participant 15)

This negative effect did not always translate into delays or stoppage of production activity, as approximately half of the respondents who acknowledged the negative effect did not report production delays. A great deal of effort and time was involved in sourcing new materials to offset the shortages as declared by almost 68% of respondents (Figure 6, Q7). There is a strong positive response (70%) (Figure 6, Q9) to the question related to whether the pandemic influenced how their organisation approached material availability but less of a conclusive trend regarding approaches to revalidation and future validation. This is supported by participant quotes (see Table 1 in Appendix 2), as below:

“Due to no availability of critical reagents, material or components from qualified suppliers/vendors, production and shipping schedules had to be rearranged. In some cases, alternative material/components had to be sourced and qualified with additional quality/technical risk assessments thus an increase in change control activity” (Participant 22)

Organisational challenges, solutions and future direction

The qualitative questions in free-text boxes (see Table 3 in Appendix 2) gave the participants the opportunity to describe challenges experienced in relation to the manufacturing and supply of non-Covid-19 medicines during the pandemic, while reflecting on technical, political, social or emerging challenges. In one case, they were questioned regarding ideas to reduce the risk of shortages due to supply chain issues moving forward. These questions have provided similar themes seen in the previous question sets, such as the challenges of working with China, who is a major manufacturer of active pharmaceutical ingredients (APIs), due to their strict restrictions:

“Hesitancy to work with China based CDMO’s due to travel restrictions. Unable to perform tech/quality visits” (Participant 9)

Other themes included the disruption caused to the supply chain and the theme of nationalised approaches by certain states created a challenge in terms of supply:

“De-prioritisation due to Covid-19 vaccine supply. Also challenges with nationalization approach by certain states” (Participant 11)

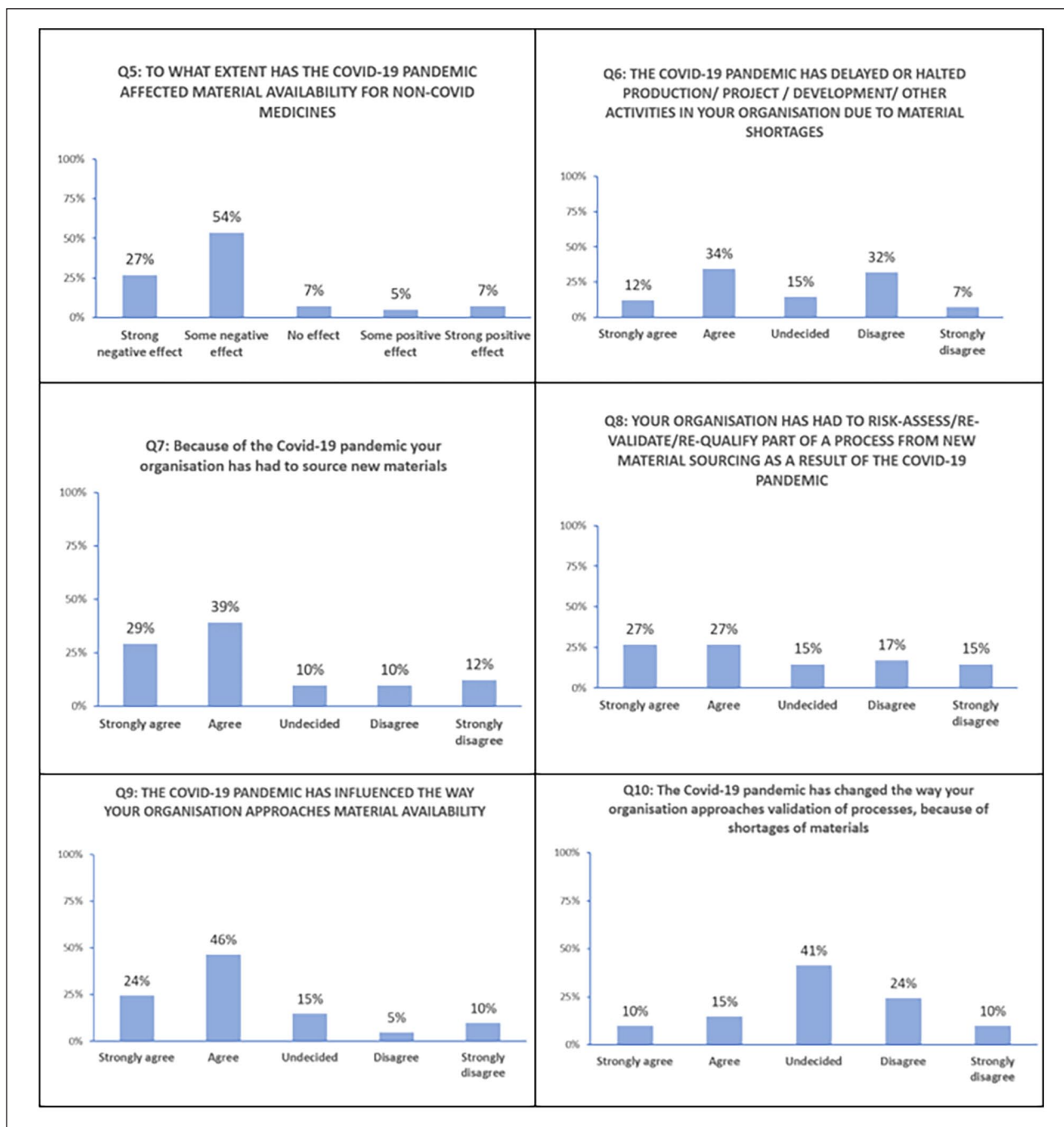


Figure 6. Survey questions concerning the impact of pandemic.

From a social aspect, the stress of keeping processes going appears evident in the responses, along with an acknowledgement of the need to keep graduates coming into the industry. Q16 looked more at the solutions side, moving forward. Some interesting themes are mentioned ranging from better planning, better use of Lean tools, dual sourcing, increasing stock levels and increased bulk ordering. Also mentioned is the desire

for flexible working arrangements to allow for continuity of work:

“Adapting to working from home in relation to QP release of materials” (Participant 19)

“Lack of staff due to sickness, social distancing affecting day to day meetings, group projects held off due to working

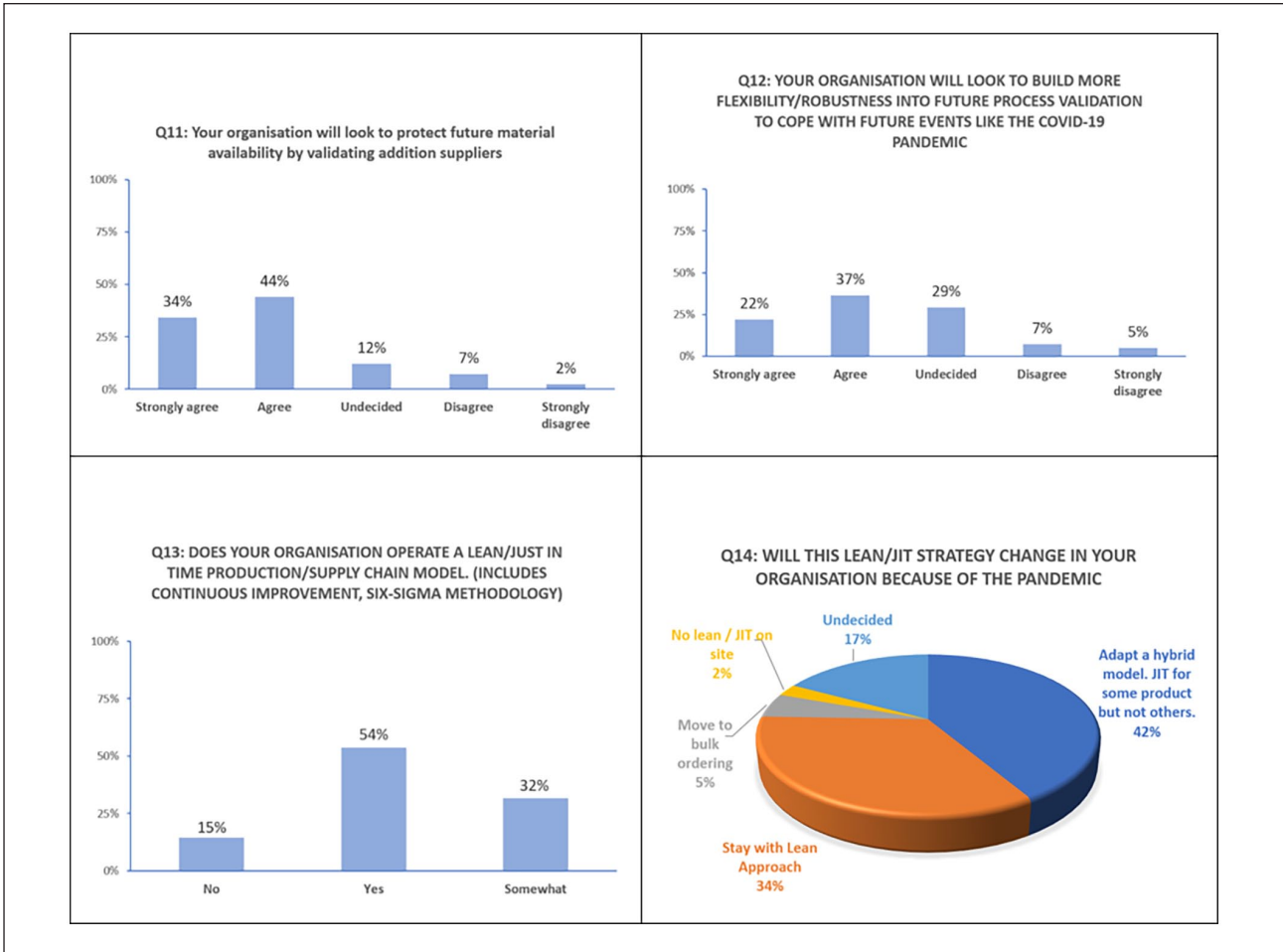


Figure 7. Survey questions concerning organisational future direction.

from home or implemented shift within certain groups” (Participant 12)

The final set of questions (Figure 7) looked at how organisations considered protection against future shocks to the global industry like the Covid-19 pandemic, exploring how organisations would look to protect future material availability. This is also surveyed in the context of Lean practice and JIT manufacturing and the survey’s aim was to question whether this approach would be maintained or adapted in future years.

The responses indicate that the immediate trend seen in the previous data sets of sourcing new or replacement material will continue with most respondents (78%) (Figure 7, Q11) looking to source new material by validating additional suppliers. Further to this, almost 60% (Figure 7, Q12) of respondents agreed that their organisations will look to build more flexibility or robustness into future validation processes to cope with future events:

“Organizations are more aware now and will take other options into account whereas they may not have previously” (Participant 8)

“We always try to validate with flexibility” (Participant 20)

With reference to the previous data set, it is shown that there is more willingness to modify the ‘validation approach’ going forward. As seen in data set Q5–10, retrospective revalidation did not score as highly. Most organisations reported that they operate a Lean/JIT production/supply chain model and 42% (Figure 7, Q14) of respondents confirmed that they would look to adapt a hybrid model, JIT for some products but not others:

“Continue the lean method with variability there in the case where lean cannot be adhered to, and bulk ordering is required” (Participant 12)

“Hybrid work practices” (In relation to Lean and JIT) (Participant 30)

Whether this represents a change in how Lean/JIT is perceived by the pharmaceutical industry remains to be seen but what is evident is that the Covid-19 pandemic has provided enough of a shock to the supply chain network to encourage organisations to think about ways to strengthen the supply chain and ensure continuous production. An example of some of the commentary from respondents can be seen in Table 2 in Appendix 2.

Response rates

Response rate/non-response rate as described in the survey plan is not possible to determine, however, the extent of the sample audience and variety of responders can be determined from the data obtained in the initial survey questions and from the analytics on LinkedIn. A total of 937 impressions were made on the survey post on LinkedIn. Confirmation of the variety of potential responders was gained from the analytics on LinkedIn, illustrating that not all responders come from the same company, region or working background. The variety of responders can be confirmed by the answers to the initial four questions from the survey, which shows an adequate spread of data.

Discussion

Organisational impact: How manufacturers managed and recovered

The COVID-19 pandemic caused an obvious strain on the healthcare systems of most countries,²⁸ but supply chains were also put under severe strain.²⁹ The present study corroborates such claims with the majority of participants (81%) declaring that the pandemic had a negative impact on material availability which in some cases (almost 50%) delayed or halted production. Fonseca and Azevedo,³⁰ also highlight how poorly insulated the global supply chain was against events like the pandemic. Shortages have always been common for a variety of reasons, but the pandemic amplified this problem and introduced several new factors that added further strain; for example, increased demand for certain components, lockdowns, difficulty in cross border travel and countries holding onto or stockpiling medicine supplies.^{29,31} Interestingly, the results showed that in the Irish pharmaceutical landscape, a lot of this impact was mitigated by companies sourcing alternative materials (68%). This enabled the full impact of the pandemic to be softened but did result in a significant increase in organisational workload and planning.

Strategic changes to practice

As seen in detail in the results section, the study participants provided ideas and solutions to the challenges faced during the Covid-19 pandemic. These solutions illustrate the need for strategic changes to practice insulating pharmaceutical manufacturing and supply chains from future crises.

Better planning and organisational management; use of operational excellence tools. Because of the added strain in organisational workload caused by the pandemic, participants highlighted the need for better planning and better use of the Lean tools. This is corroborated by previous literature. More specifically, better monitoring of supply chain weaknesses^{18,32,33} and better tracking of medicine stock levels³⁴ has been suggested from various scholars. Moreover, a study conducted by McDermott et al.³⁵ in 2021 highlighted the benefits of operational excellence methodologies and Lean and Six Sigma tools in the healthcare system. Flexible working was also highlighted by the study participants, which has been supported by the Information and Communication Technologies (ICT) as illustrated in an Indian study by Sharma et al.³⁶

A move away from Lean/JIT processes. The study provided some interesting suggestions for industry solutions, some of which suggest a move away from Lean principles and JIT manufacturing. The same idea is discussed in the study by Gereffi³¹ focusing on personal protective equipment (PPE) products in the United States during the Covid-19 pandemic, in which it is suggested that the prevalence of Lean/JIT adaptation aiming to increase efficiency and reduce cost with reduced inventories has left the global supply chain in a fragile state. This notion is being highlighted among several studies.^{31,37–39} However, Thakur-Weigold and Miroudot, in a study published in 2023, argue that the ‘too-lean’ concept is actually a myth that has been spread after the Covid-19 pandemic and the Russian invasion of Ukraine. They argue that there is no concrete scientific evidence to support such claims and that Lean/JIT processes aim to minimise waste by targeting redundant or faulty elements of production, transportation and supply.⁴⁰

Dual sourcing of materials. In addition, the concept of dual sourcing of materials arose as a solution to shortages by the study’s participants. A plus one approach, which is a way to reduce risk and diversify the supply chain network, was initially proposed to reduce the overexposure to the Chinese market and encourage investment in alternative supply chain options from other countries and markets.⁴¹ Multisourcing of materials has been also suggested by previous literature, in an essay discussing the impact of the Covid-19 pandemic on the global supply chain and pharmaceutical manufacturing by Hausmann in 2020.³⁷ Yet, dual sourcing and validating a process for multiple input options of the same material add an obvious cost to the manufacturing profile of a medicine and this is likely to result in an increase in cost and complexity which goes against the principles of the Lean manufacturing model.² This approach does, however, reduce the risk of manufacturing shutdown and is being pursued by multiple organisations. Whether this is a shift in the Lean mindset or whether the Lean mindset will have to shift to catch up with the reality of global events remains to be seen. What is interesting though is that by its very nature Lean and continuous improvement are always adapting so events like the Covid-19

pandemic may speed up this evolution. These approaches could help to formalise some of the activities seen in the Irish pharmaceutical manufacturing setting and add further structural resilience to Irish and international pharmaceutical manufacturing systems.

Sustainable local production. The concept of sustainable local production featured in the survey, similar to the ‘One Roof’¹¹ principle. The suggestion of a more regional supply chain was also highlighted by Hausmann in 2020.³⁷ This may be a logical reaction to global disruption but may not be practically possible. If we imagine the concept of the ‘One Roof’ principle of the Renault car company, which was based around a localised production unit, such a system might be more insulated from Covid-19-related supply problems. Indeed, there is a sustainability argument to be put forward about the nature of pharmaceutical production. In the future world, would more value be placed on a raw material that while more expensive, represents better value to the environment and assured supply? The causes of material and supply constraints may just be as simple as that. However, the world’s resources are not evenly distributed, and geographical and geopolitical factors will always play a role in the supply chain network.

Pivoting. Sourcing new or replacement materials and validating additional suppliers appeared as recommended future steps by the study participants. Socal et al.⁴² proposed the introduction of a metric-based system for manufacturers, in which scores are assigned based on supply chain resilience and ability to meet demand. This could encourage companies to promote more safety stock into their manufacturing plans, as suggested by the study participants (i.e. increase stock levels and bulk ordering). Such solutions have also been suggested from various scholars.^{18,34} This will require robustness into future validation processes which can be facilitated by greater supply chain transparency. Literature has highlighted that greater supply chain transparency may be required to be able to monitor potential shortages more closely and put in place measures to combat supply chain stresses from events like the Covid-19 pandemic. China and its dominant market share in the manufacture of APIs and India’s large-scale manufacturing of generic medicines which predominantly use API from China is cited as an example of a supply chain that is not fully open, or transparent for analysis.²⁹ More cooperation in the area of mapping and creating a database of API manufacturers could also help speed up the approval of new sources of API.⁴²

Theoretical and methodological implications

There are several advantages of JIT and the system is overall successful but when global events or indeed significant local events happen, this can disrupt a supply chain. If the pandemic had not occurred, the weaknesses in the system may not have been exposed to the extent that they were. With every crisis, there is an opportunity to develop and grow new ideas.¹⁸ The Covid-19 pandemic is undoubtedly

a moment in time where the pharmaceutical industry and its Lean journey is under scrutiny.

The TPS ‘House’⁴ as a metaphor is rigid, secure and stable. We suggest that the challenges the pandemic imposed highlighted the need for flexibility and better use of the Lean tools rather than discrediting them. Perhaps this could be achieved by adding flexibility to the ‘house’ metaphor and diagram by making the foundations of this house more flexible in times of a crisis. The way Lean methodologies and tools are conceptualised and used in the pharmaceutical business model could be adjusted to align more with flexibility in the times of these significant contextual shifts.⁴³ As mentioned in the study by McDermott et al.,³⁵ such events are so rare (0.001%) that do not justify the abandonment of a theoretical framework that has advanced business practice. Our theoretical contribution is simply underlying the importance of flexibility in the Lean/JIT model. We also propose that the framework should be re-examined to establish how this flexibility could be incorporated into the TPS House model.

Conclusion

It can be concluded that the pharmaceutical industry is a firm practitioner of the Lean and JIT principles and it experienced material and supply chain issues associated with non-covid medicines. During the pandemic, the industry pivoted and adapted its standard supply chain business model practices to manage the impact of the pandemic. The Covid-19 pandemic has shocked this sector; however, Irish pharmaceutical manufacturing demonstrated evidence of resilience throughout the pandemic. The pandemic has also made the industry evaluate its future business model, and a further evolution of the supply chain model may surface. In the spirit of continuous improvement, we encourage future research to explore how the modification of JIT/Lean model will be achieved, adding flexibility to the TPS house, to ensure that public health is not disrupted during future global events like the Covid-19 pandemic.

Limitations and future scope

This study has several limitations; the number of participants is limited and is representative only of the Irish pharmaceutical industry. We suggest that similar research studies with larger sample sizes in different geographical locations would be useful to identify if similar effects were present in larger countries. Moreover, the self-reported survey design has its own limitations and even though it is suitable for initial exploration of research topics, future studies could use more complex research designs that use multiple data sources to explore the proposed variables.

Declarations

Ethics approval and consent to participate

Ethical approval was sought from Trinity College Dublin and consent to participate was taken before data collection.

Consent for publication

Not applicable.

Author contributions

Michael Howlett: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Eleni Niarchou: Data curation; Formal analysis; Project administration; Writing – review & editing.

Bernard D. Naughton: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Availability of data and materials

All available data is presented in this publication or its appendices.

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Appendix I

Survey questions

Q1: What geographical region of Ireland is the company you work for located?

- A: Ulster
- B: Munster
- C: Leinster
- D: Connacht
- E: Outside of Ireland

Q2: Within which area of the pharmaceutical industry do you currently work?

- A: Supply Chain
- B: Quality
- C: Operations
- D: Validation
- E: Other please specify

Q3: What category of product do you produce at your facility/virtual facility?

- A: Active Pharmaceutical Ingredient (API) for small molecule manufacturing
- B: Drug Substance (for biologics manufacturing)

- C: Drug Product (biologics or small molecule)
- D: Other, please specify

Q4: Does your facility/virtual facility manufacture Covid-19-related or non-Covid-19-related medicines?

- A: Manufactured Covid-19 related medicines
- B: Manufactured non-Covid-19 related medicines
- C: Both A and B

Q5: To what extent has the Covid-19 pandemic affected material availability for non-covid medicines (i.e. raw materials/components/disposable-technology/filters/equipment/reagents) in your organisation.

Strong Positive effect	Some Positive effect	No effect	Some Negative effect	Strong Negative effect
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

To what extent do you agree with the following statements.

Q6: The Covid-19 pandemic has delayed or halted production/project/development/other activities in your organisation due to material shortages.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q7: Because of the Covid-19 pandemic your organisation has had to source new materials (raw materials/components/disposable-technology/filters/equipment/reagents)

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q8: Your organisation has had to risk-assess/re-validate/re-qualify part of a process from new material sourcing as a result of the Covid-19 pandemic.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q9: The Covid-19 pandemic has influenced the way your organisation approaches material availability.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q10: The Covid-19 pandemic has changed the way your organisation approaches validation of processes, because of shortages of materials.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q11: Your organisation will look to protect future material availability by validating addition suppliers.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q12: Your organisation will look to build more flexibility/robustness into future process validation to cope with future events like the Covid-19 pandemic.

Strongly agree	Agree	Undecided	Disagree	Strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q13: Does your organisation operate a Lean/Just in time production/Supply chain model. (Includes Continuous Improvement, six-sigma methodology)

Yes	Somewhat	No
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If possible, please provide further detail;

Q14: Will this Lean/JIT strategy change in your organisation because of the pandemic.

- A: Stay with Lean Approach
- B: Move to bulk ordering
- C: Adapt a hybrid model. JIT for some product but not others.
- D: Other. Please state

If possible, please provide further detail;

Q15: Please describe the challenges you experience in relation to the manufacturing and supply of non-covid medicines during the pandemic. Please reflect on the technical, political, social or emerging challenges.

Q16: What ideas do you have to reduce the risk of shortages due to supply chain issues moving forward.

Appendix 2

Supporting quotes for study survey

Table 1. Survey Q5-Q10 impact of pandemic: supporting quotes.

<p>'Long lead times on equipment and raw materials'. (Participant 28)</p> <p>'Some materials particularly coming from China were delayed. As well as this some of our suppliers would have sourced materials from China in manufacturing materials for us, so that had a knock-on effect and meant further delays'. (Participant 23)</p> <p>'Lack of staff due to sickness, social distancing affecting day to day meetings, group projects held off due to working from home or implemented shift within certain groups'. (Participant 12)</p> <p>'Due to no availability of critical reagents, material or components from qualified suppliers/vendors, production and shipping schedules had to be rearranged. In some cases, alternative material/components had to be sourced and qualified with additional quality/technical risk assessments thus increase in change control activity'. (Participant 22)</p> <p>'Had to ensure we have 2 back up suppliers for each raw material instead of 1'. (Participant 6)</p> <p>'Reliable vendors no longer able to ensure product availability so other vendor relationships have had to be set up in order to maintain production'. (Participant 12)</p> <p>'We are reviewing implementation additional redundancy in our supply chain'. (Participant 38)</p> <p>'Largely unchanged in appetite for risk but we look at more parallel ways of working now'. (Participant 38)</p> <p>'No change to process validation'. (Participant 28)</p>	<p>'Delays to critical filters & assemblies'. (Participant 27)</p> <p>'Caused a hard stop in facility for 6 months due to component shortage'. (Participant 15)</p> <p>'no lost production slots as a result of material constraints due to covid. However, we have had some delays due to material releases at the last minute, additional work for change controls to allow use of alternative materials or assemblies'. (Participant 21)</p> <p>'Production schedules reworked to accommodate delays in supply chain'. (Participant 27)</p> <p>'Most suppliers and CMOs had good countermeasures in place'. (Participant 7)</p> <p>'It was found that most suppliers of incoming materials to our company had been effected by COVID-19 and it was not worth sourcing/ qualifying a new supplier'. (Participant 16)</p> <p>'Mainly risk assess use of new part or material as opposed to revalidation of part of a process'. (Participant 17)</p> <p>'Validation processes, for the most part, remained as they were before'. (Participant 16)</p>
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Table 2. Survey Q11-Q14, future organisational direction: supporting quotes.

<p>'Current project ongoing assessing new suppliers'. (Participant 6)</p> <p>'Certainly, more proactive risk mitigation has been deployed'. (Participant 11)</p> <p>'Dual sourcing of more difficult to acquire materials'. (Participant 28)</p> <p>'Likely that additional risks will be considered in future'. (Participant 7)</p> <p>'We always try to validate with flexibility'. (Participant 20)</p> <p>'We are increasing our pre-campaign check times to ensure we can receipt required materials ahead of manufacture. This is to account for increased lead times in order/receipt'. (Participant 5)</p> <p>'More bulk ordering occurred because of the pandemic'. (Participant 18)</p>	<p>'Single suppliers are to be avoided if at all possible'. (Participant 10)</p> <p>'Double supply is now a pillar of our business continuity plan'. (Participant 16)</p> <p>'Expect consolidation of suppliers within network'. (Participant 30)</p> <p>'Organizations are more aware now and will take other options into account whereas they may not have previously'. (Participant 8)</p> <p>'Hybrid work practices'. (Participant 30)</p> <p>'Continue the lean method with variability there in the case where lean cannot be adhered to, and bulk ordering is required'. (Participant 12)</p> <p>'Redundancy in API bulk through larger stocks'. (Participant 38)</p>
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Table 3. Survey Q15-Q16 challenges and future risk: supporting quotes.

Q15	Q16
<p>'Hesitancy to work with China based CDMO's due to travel restrictions. Unable to perform tech/quality visits'. (Participant 9)</p>	<p>'Proposed revision of ICH Q9 requires companies to risk assess SC / processes to mitigate against supply disruptions. Global update of this process should reduce risk to patients'. (Participant 4)</p>
<p>'De-prioritisation due to c19 vaccine supply. Also challenges with nationalization approach by certain states'. (Participant 11)</p> <p>'Having people available on site when out with Covid'. (Participant 14)</p>	<p>'Increase stock levels internally of consumables, reorder levels'. (Participant 5)</p>
<p>'at times it was operating at a hand to mouth with heavy micromanagement to avoid dropped batch slots or batches in progress due to shortage of components or raw materials'. (Participant 15)</p>	<p>'Perhaps a group across a few pharma companies could be set up to discuss their suppliers and issues companies are having with raw materials. Help each other out'. (Participant 6)</p>
<p>'Validating new processes due to extremely long lead times for certain manufacturing inputs'. (Participant 18)</p>	<p>'Ensure risks to supply are considered during vendor selection. Good vendors will respond to such requests by supplementing robustness in their internal processes'. (Participant 7)</p>
<p>'Adapting to working from home in relation to QP release of materials'. (Participant 19)</p>	<p>'Ensure robust supply of raw materials by dual supplying and ensuring they are located in different countries'. (Participant 9)</p>
<p>'Resourcing and material supply is the key issue the bigger you are the better'. (Participant 20)</p>	<p>'Dual sourcing, for items like single use reduce bespoke elements, try and source more off the shelf inputs rather than bespoke. To address geographical challenges ensure multiple supply nodes aligned with country e.g. EU supply for EU mfg nodes. Companies could also prioritize product manufacturing to assist with supply chain management at network level to assist sites'. (Participant 11)</p>
<p>'Constant stream of supplier changes as companies try to secure raw materials and components'. (Participant 25)</p>	<p>'Have kanban system in place to ensure availability of stock always'. (Participant 12)</p>
<p>'Sickness continues to disrupt manufacturing schedules and this will get worse through the winter as covid is not gone but no restrictions. Also difficulty attracting talent to the site which has not embraced remote or hybrid working'. (Participant 28)</p>	<p>'Bring outsourced testing back in house'. (Participant 14)</p>
<p>'Need more science graduates coming through'. (Participant 30)</p>	<p>'Forward planning and detailed look ahead with departments working together in terms of assessing if a filter etc is commonly used across site. More collaborative approach in the industry as a whole. Better comms between us and suppliers in terms of delivery dates and volumes'. (Participant 15)</p>
<p>'Non direct Covid Medicines have also seen a large increase as result of the pandemic. This has put a significant pressure on supply chains to readjust to shifting demand'. (Participant 38)</p>	<p>'Better forecasting and back up approved suppliers'. (Participant 19)</p>
	<p>'Self-manufacture'. (Participant 20)</p> <p>'Network consolidation of site supply chains'. (Participant 30)</p>
	<p>'Better planning'. (Participant 36)</p> <p>'Manufacture of large quantities of bulk API/Drug products coupled with flexible or generic packaging for flexible delivery'. (Participant 38)</p>

Appendix 3

Survey information leaflet

Study Title:

The impact of the COVID-19 pandemic on pharmaceutical supply chains and the production of non-Covid-19-specific medicines

Study Organiser:

Michael Howlett, Post Graduate student in MSc/Diploma Pharmaceutical Manufacturing Technology,



Dear Participant,

You are being invited to take part in a research survey that is being conducted as part of a post graduate master's dissertation. Before deciding whether you wish to take part, please read this information leaflet. No personnel information or sensitive business data is being requested as part of this survey. All responses will be anonymous. Further information is provided below.

Thank you for your time.

Survey and study detail

Why is this survey being conducted? This survey is being conducted as part of a data gathering exercise for a master's dissertation study into 'The impact of the COVID-19 pandemic on pharmaceutical supply chains and the production of non-Covid-19 specific medicines'. The survey is one element of the dissertation which also involves a literature review. The aim of the survey is to measure real-world experience and data from the local pharmaceutical community. The survey will be used to compare against documented global patterns.

Why am I invited to partake in this survey? You are being invited to partake as a relevant cross section/target audience that is involved in the Irish pharmaceutical industry. Your

experiences of working during the COVID-19 pandemic and how you/your employer were impacted is relevant to the research study. This study is relevant if you are over 18 years of age and are employed in the pharmaceutical industry, in a quality, supply chain role, or experience related to supply of medicines that can be impacted by pandemic-like emergencies. Including virtual roles managing activities related to manufacturing.

How will the survey be conducted? A set of questions has been designed to measure the participants' experience of supply chain disruption during the COVID-19 pandemic. The questions are multiple choice and there is a free-text option to add additional information if required. The Survey is completely anonymous and no personal or business data will be captured or stored. Please avoid adding detail that may identify where you work. Please keep responses general but relevant. Participation in the survey confirms consent that you as the participant is willing to partake. Once survey is started withdrawal may not be possible.

Will my details remain confidential/will the survey be GDPR compliant? No personal or business-sensitive questions are being asked as part of the survey. The survey will be conducted via online survey. After the completion of the study, all data will be downloaded and deleted. No e-mail or IP addresses will be retained.

What will happen to the results of this research? The results of the survey will be analysed and reported in an academic dissertation. It may also be published in a peer-review journal, presented to the pharmaceutical industry community, or used for teaching purposes.

Please click the link if you agree to participate and confirm you have read and understood the Information Leaflet for the above study, and consent to being involved in this study. Please complete this survey within 1 week of receiving invitation to facilitate report writing. Any questions may be directed as a response to this e-mail.

Thank You,
Michael.