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Current Perspectives on the Development of Industry 4.0 in the Pharmaceutical Sector

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Highlights:

- Investigation to determine current 4.0 adoption in the pharma/biopharma sector.
- Irish pharma/biopharma sector is highly representative of the global sector.
- Detailed perspective of current and projected levels of 4.0 adoption.
- Knowledge & involvement of 4.0 implementation is lacking across industry sector.

Current Perspectives on the Development of Industry 4.0 in the Pharmaceutical Sector

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Abstract

Industry 4.0 is a concept that represents the adoption by industry of techniques and processes allowed by digitisation, cloud computing, the internet of things and big data to gain competitive advantages in domestic and global markets. The research is conducted in Ireland with the resulting data examined through a global lens, yielding information relevant to the effective adoption and integration of 4.0 concepts. Key outcomes are the perspectives of the pharmaceutical and biopharmaceutical industries with regards to the adoption of 4.0, the current level of implementation of 4.0 technologies in manufacturing facilities and planned 4.0 projects to be executed. Statistically relevant relationships evident in the responses are also investigated. This research provides novel and highly relevant information concerning the state of industry preparedness for the adoption of 4.0.

Across all survey respondents only 42% indicated any knowledge of 4.0. The majority of respondents who indicated a knowledge of 4.0 identified with either the Automation or Engineering department. Among established employees with greater than 8 years of experience 82% identified with having knowledge of 4.0. Those surveyed with Vice-President or Director roles, had a 98% certainty of 4.0 awareness. A noteworthy finding of this work is the identification of a substantial disconnect in knowledge of 4.0 based on seniority, function and industry. Thus while the implementation of 4.0 is playing an increasingly significant role in the modernisation of the Pharmaceutical and Biopharmaceutical industries, challenges remain with respect to the holistic fusion of 4.0 into the culture of organisations.

Keywords: Industry 4.0; 4th Industrial Revolution; Pharma 4.0; Irish Pharmaceutical Sector; Survey

1. Introduction

Industry 4.0 is considered a new industrial stage in which several emerging technologies are converging to provide digital solutions. Recent research conducted by [1] investigated the implementation of 4.0 in 92 manufacturing facilities to better understand its adoption by industry. The work proposed a conceptual framework for these technologies, which are separated into front-end and base technologies. Front-end technologies consider four dimensions: Smart Manufacturing, Smart Products, Smart Supply Chain and Smart Working, while base technologies consider four elements: internet of things, cloud services, big data and analytics. The results also show that the implementation of the base technologies is challenging companies, with big data and analytics having a relatively low employment in the sample studied.

The pharmaceutical and biopharmaceutical sector has seen a significant changes in its operating model and footprint over the past couple of decades according to [2]. Several studies have reviewed the industry's declining productivity [3, 4], the transitioning of commercial models [5] and the growth of emerging markets as key revenue contributors [6]. The current pharmaceutical model is transitioning to that of a lean, focussed entity with a research footprint within key innovation bio-clusters and a growing revenue stream from specialty products and biologics through emerging markets. In addition, [5] considers that the pharmaceutical sector is going to encounter more stringent regulatory pathways for approval of new drugs, as well as closer government scrutiny of the continued marketing of existing drugs. There is little doubt that the regulators are going to focus increasingly on patient safety and benefits when bringing new drugs to market [7].

A particular focus on research and development (R&D) of pharmaceuticals is evident in research by [8], as the drug development period is regarded as the critical factor in determining success. This unique characteristic of the industry is due to R&D activities that include clinical trials and approval of the regulatory authorities, which require long time durations, combined with the strong desire of companies to sell the product within its patented time frame. In Japan, the duration of the R&D development is in the range of 9–16 years, whereas patent protection normally lasts 20–25 years [9]. The average cost of developing a new drug is estimated to be about 1.0–1.2 billion USD, including expenditure on failed projects [10].

The convergence of IT and healthcare is another area that will influence the big pharma model over the coming years according to [2]. Big data and mobile health are starting to transform healthcare and diagnostics in a significant way, with new players such as Apple and Google acting as increasingly disruptive catalysts. Medicines paired with companion diagnostics have been a successful strategy to gain market access, with firms such as AstraZeneca, Roche, Novartis and Sanofi progressing as much as 60–80% of their clinical portfolios with companion diagnostics. In the personalised and precision medicines era, this strategy will probably translate into medicines accompanied with apps or wearable devices that help patients monitor key parameters and manage their diseases.

Research conducted by [11] explored augmented reality (AR) and its impact on the pharmaceutical industry. AR enables bridging the gap between the physical world and the increasingly important digital environment. Currently, the compound annual growth rate (CAGR) of the industrial AR market is projected to be around 74% between 2018 and 2025. The global market for AR and VR is projected to reach $814.7 billion by 2025 [12]. This significant growth is likely to be sustained or accelerated as the AR technology matures and the variety of applications within the industry broadens. While the importance of AR is widely accepted, recent research has shown that the implementation for industrial applications is challenging [13].

This research is based in Ireland but is highly representative of the global industry and provides an ideal singular location to assess the impact of 4.0 without any geo-political or cultural confounding influences. The pharmaceutical and biopharmaceutical industries in Ireland generated €67.8 billion exports in 2017 [14], up 2% from 2016. Using a bespoke survey the research aims to highlight topics such as the current level of adoption of 4.0 technologies in Ireland among pharmaceutical and biopharmaceutical companies, as well as related industries such as consulting and medical devices. It also explores corporate outlook on 4.0 and the future, as well as planned projects and in-house technological advancements.

A literature review on the subjects of Industry 4.0, Pharma 4.0 and related topics, identify a lack of detailed published information on the preparedness of industry to adopt 4.0 technology was noted. The review conducted by [15] states that in his analysis of 33 papers relating to Pharma 4.0, only six of the papers (18%) were survey or interview based. Current research data available is not specifically on the topic of Pharma 4.0, or not in-depth enough to provide cogent information on 4.0. By conducting a comprehensive industry survey, this research provides a novel insight into the adoption of 4.0 by the Irish pharmaceutical/biopharmaceutical and medical devices industries; world leaders in this industry sector. The research was designed to examine the levels and differences in adoption between pharmaceutical, and biopharmaceutical – as well as providing a space for the personal viewpoints of industry professionals towards 4.0.

One particularly relevant survey was conducted by the International Society of Automation (ISA), for their InTech Magazine publication in the May/June 2018 issue. Its purpose was to find out how aware people were of the terms “Internet of Things” and “Industry 4.0”. While this research mostly focussed on the effects of Industry 4.0 on industrial manufacturing, there was valuable insight into the viewpoint of members of industry with regards to technologies involved and the Industry 4.0 implementation. The work of the ISA highlighted two broad categories: improved communications and data transfer, and transformational concepts and technologies for manufacturing. The question style and direction of the research conducted by the ISA formed the basis for this industry survey.

Another survey was conducted by AVEVA – a British multinational information technology company – in association with independent research firm Vanson Bourne – an independent market research partner –; the report is titled "Digitalisation in Chemicals & Petrochemicals"[16]. Whilst it was not focussed on the Pharmaceutical industry, this research yielded thought-provoking approaches to gathering information – such as using a combination of telephone interviews and online questionnaires to capture the opinions of several industry leaders with job titles such as Director, Chief Officer and Manager. Some interesting questions were also posed to the respondents. These included questions regarding the interviewee's personal opinion or viewpoint of certain issues as well as questions regarding the respondent's organisation's approach to modern Industry 4.0 technologies and methodologies. By utilising this approach, AVEVA's report offers a glimpse into a large number of industry's facets, therefore allowing one to identify possible gaps that can be filled with suitable research.

The objective of this research is to scope out the current level of 4.0 adoption in Ireland and worldwide, and to provide a base of information to both industry and academia. The information presented can be used to deduce the strategy and direction that industry may take.

1.1. Survey Design

Research conducted by [17] indicated factors necessary in order to receive a high response rate: pre-notification sent by email (91.8%); survey structure – an email with a clear research subject heading (87.4%); professional email invitation (85.1%); short and concise question items (94.1%); few or no open-ended questions (57%); and a reminder (66.6%). The results of this study suggest that participants prefer completing electronic surveys received mostly from students, colleagues and authority figures (e.g. department chair or higher) compared to people from other organisations who they do not know personally or professionally. Results also indicated that the survey response rate was highly related to the research interests of participants. Over 88% of participants indicated that they would be more likely to complete a survey if they are interested in the topic. More than three quarters of participants, (78.3%) reported that the study should assure anonymity and confidentiality for the information they share with researchers in the survey.

The survey software most suitable to the requirements of this survey was found to be Google Forms due to its ability to remain anonymous, its highly customisable layout, and its proven reliability in collecting data as noted during the pilot run. This was therefore chosen to be the survey hosting platform.

2. Research Methodology

2.1. Survey Layout

The survey for this work consisted of 25 clear, non-biased questions. Questions were structured to encourage the respondent to express their professional opinion through open-ended questions as well as specialised formats. One such format is the Likert scale. This style of question are typically used to represent attitude towards a topic. Research conducted by [17] indicated that 94.1% of respondents were more likely to complete a survey if the questions were short and concise. Similarly, respondents were more likely to complete a survey if they knew how long it would take to fill out beforehand. With a 91.1% success rate if the survey could be completed within 15 minutes.

The survey is formulated to include sections, providing natural breaks in the flow of ideas with a change of topic. This formatting structure provides an organic approach to the information to make the survey more engaging. This is due to the questionnaire seeming shorter than it actually is, and increasing the response rate. The inclusion of sections also allows for branching of the questionnaire depending on the respondent's answer to a specific question; this prevents respondents being exposed to some questions, which may not apply to them and allows for a higher survey customisation.

The survey questions were categorised in one of two categories as shown in Table 1.

Personal indicators			**Response**
Respondent	*Company*		4.0 projects currently implemented
Level of experience	Type:	Pharmaceutical	Future 4.0 projects planned
Role in company		Biopharmaceutical	Corporate outlook on 4.0
Primary department		Medical Devices	Confidence in implementing 4.0
	Primary manufacturing type		Benefits & challenges of 4.0
	Location		Involvement with 4.0 adoption
			Current level of adoption of 4.0

	Key trends influencing adoption of 4.0
	Desirable skills for new hires
	Main areas of focus for 4.0 adoption

Table 1 - Personal indicators and response section question topics

A pilot survey was shared with a selected number of representative personnel from the various industry sectors for their input prior to the completed survey being circulated. The respondents indicated the questions were suitably direct and thought provoking and would be happy to respond to such a questionnaire.

2.2. Distribution

It has been identified that personalisation of invitations using greetings, titles, and addresses significantly increased response rate [18]. Requesting assistance from those surveyed is influential in increasing response rate [19]. Individuals were more likely to respond to survey requests from authority figures or if they were addressed as a part of a particular selected group chosen to complete the survey [20].

Research carried out by [17] found that survey responses increased for research carried out by a student – with 51.5% of their respondents more inclined to complete the survey if it is by a student for research purposes. A key factor in survey success is that 88.7% of respondents indicated they were more inclined to answer a survey if received from a colleague they know. A similarly high response rate of 88.2% was noted for surveys which studied a topic the respondent had a vested interest in, and 76.3% of respondents were more likely to fill in an academic survey. With regards to the first impression of the survey, respondents to the [17] research survey showed respondents were more likely to open an email with subjects clearly indicating the research nature of the content and more likely to fill out the survey if the email invitation looked professional, at 87.4% and 85.1% respectively. This information contributed significantly to the design and selection of distribution pathway for this research.

2.2.1 Industry contacts

Distribution using industry based professional bodies was invaluable at the outset of the survey, as it provided access to the network of pharmaceutical, biopharmaceutical and medical devices professionals targeted for the questionnaire. The primary industry contacts used for distribution were:

- BioPharmaChem Ireland (BPCI), a branch of the IDA (formerly the Industrial Development Authority)
- The International Society for Pharmaceutical Engineering (ISPE)
- The Institution of Chemical Engineers (IChemE)
- The International Society of Automation (ISA)
- The Irish Medtech Association (IMDA)

2.2.2. Network distribution

Respondents were asked to forward the circulation email to colleagues, leading to a more extensive distribution than what could be achieved otherwise. As stated briefly previously from [17], 88.7% of respondents were more inclined to answer the survey if they received it from a colleague they know. Due to the nature of the target respondents, direct communication with unknown contacts was not a possibility. This pathway led to a better exposure of the research being carried out, and greater interest was taken in the possible outcomes of the research.

2.2.3. LinkedIn

Survey circulation via LinkedIn Messaging and Networking platforms was also explored. LinkedIn allows for direct contact with otherwise unreachable members of industry, albeit foregoing a certain level of anonymity. For the purposes of the distribution of this survey, LinkedIn was used minimally.

2.2.4. Alumni

Utilising the network of Process and Chemical Engineering alumni at University College Cork, this survey was distributed to companies through their current or past employees. Alumni were also more likely to complete and distribute the survey, as they had a connection to the department. In total, 406 email addresses were sourced from the department, comprising of 21 years of alumni.

3. Survey results

The survey received 78 replies from respondents which were representative of the Irish multinational sector, and therefore global, manufacturing scene. Survey analytics were generated automatically by the Google Forms software, providing visual representations of the results through the use of bar charts, pie charts and histograms. The data was exported to Microsoft Excel and StatSoft Statistica for analysis. Fisher's Least Significant Difference (LSD) was utilised to identify key outcomes and statistically significant relationships. Graphical display of results was used to clearly identify responses and trends in responses.

From the analysis, further trends were extracted to reflect general viewpoints of a certain part of industry, or of a particular role towards 4.0. Significant findings are collated and discussed in General Findings. Although the inclusion of 4.0 concepts is a major consideration for any modern process development, Figure 1 indicates that only 33 (42%) of the respondents specified they had knowledge of 4.0. Given the pre-eminence of 4.0, it is surprising that a majority of those surveyed (58%) had not heard of 4.0, raising an interesting question as to why 4.0 is not known more widely. One possibility might be an industrial silo mentality, where sharing of information across departments is perhaps less than ideal. This deficit in information sharing may also explain why the majority of the respondents that indicated knowledge of 4.0 were also in managerial roles such as manager, vice-president or director, at 70% as shown in Figure 2a.

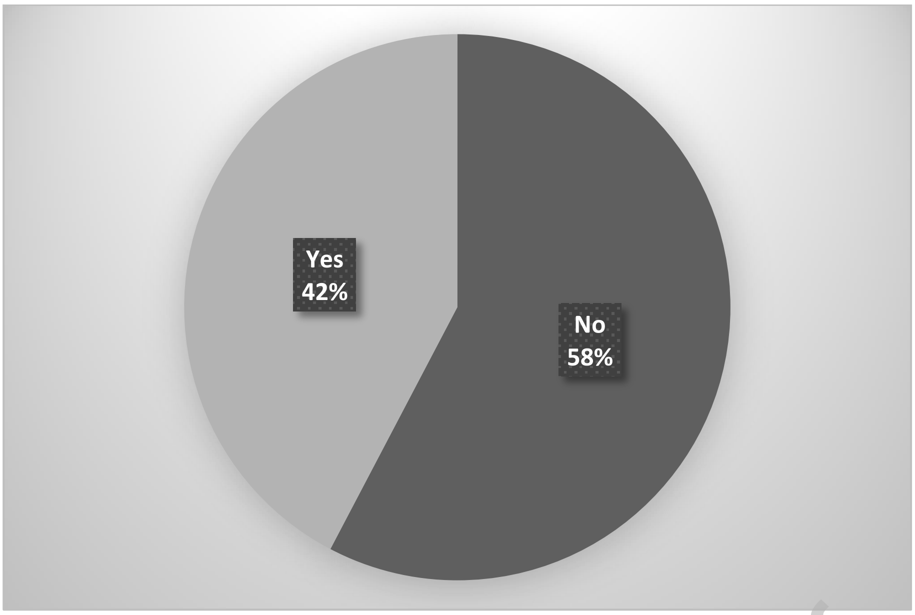

Figure 1 – Level of awareness of 4.0 among Irish respondents in 2019, n=78

Research by [21] shows that successful implementation of knowledge in organisations needs employees with sufficient knowledge about the methods and principles of the technology to be implemented. The mediation of these skills during ongoing production is known as an efficient concept with consequences being additional cost and time pressure.

With respect to location within Ireland, 67% of respondents who were aware of 4.0 are located in the Munster region, 27% are located in Leinster and the remaining 6% are located across other locations in Ireland. This can be attributed to the Munster region being a very significant pharma hub combined with the proximity and strong association with University College Cork.

The majority of the respondent pool with knowledge of 4.0 are associated with the pharmaceutical and biopharmaceutical industries (52% and 30% respectively) identified in Figure 2b. The remainder (18%) comprised of medical devices, consultancy and other industries. This is certainly a reflection of manufacturing in Ireland, with a large percentage of manufacturing facilities being pharmaceutical and biopharmaceutical facilities.

Level of exposure to 4.0 is explored in Figure 2c, showing that 55% of the respondent pool with knowledge of 4.0 had greater than 15 years of experience, 27% had between 8-15 years of experience and the remaining 18% had less than 7 years of experience. This alignment between experience and

4.0 points to a stratified knowledge layering within the industry with the majority of the respondents that indicated knowledge of 4.0 also in managerial roles such as manager, vice-president or director.

Figure 2d shows that a large percentage of manufacturing facilities focussed on API production. Of the respondent pool with knowledge of 4.0, 55% are employed in the primary production of API's, 21% in secondary or downstream manufacturing, while the remaining 24% are employed in a complete manufacturing facility (both primary and secondary), consultancy/design, medical device components or other.

Figure 2e shows that of the respondent pool with knowledge of 4.0, 28% are associated with Engineering, 27% with Operations, while the remaining 45% are associated with Automation, Process Development, Research and Development, Quality and Other. Of the replies for Operations, 3 answers comprised of Operational Excellence roles. When comparing the responses of Role and Function, it was noted 43.5% of Engineering and Operations function respondents held roles such as Manager, Director and Vice-President.

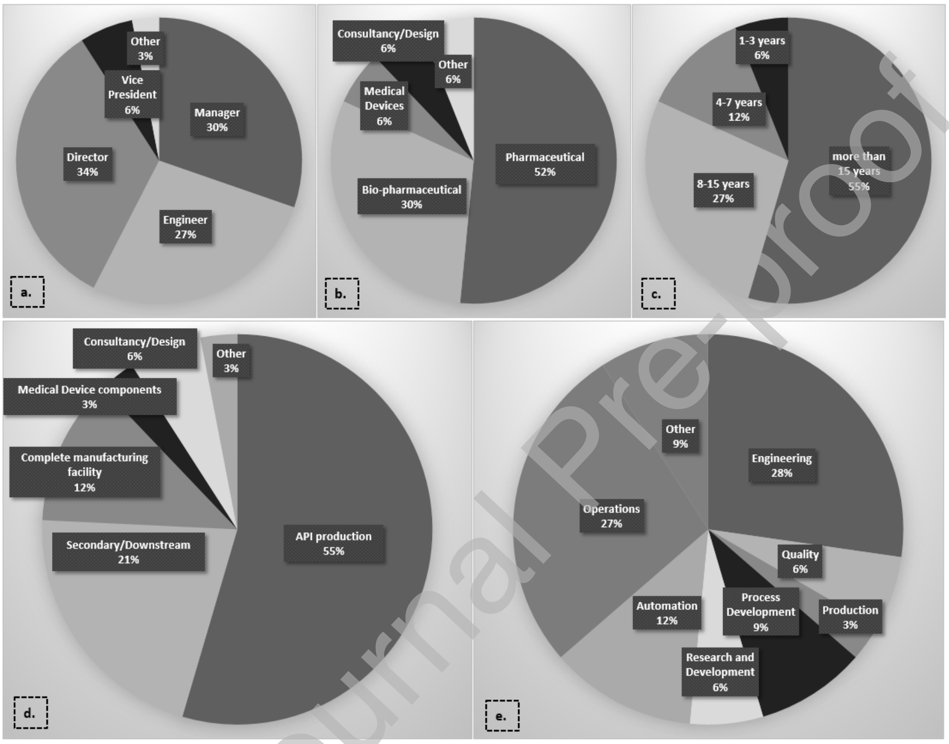

Figure 2 - Visual representation of respondents aware of 4.0 to various survey questions, n=33

(a – executive function, b – industry sector, c – experience level, d – primary manufacturing type, e – primary department)

With respect to the respondent pool, which indicated having a knowledge of 4.0, other observations include:

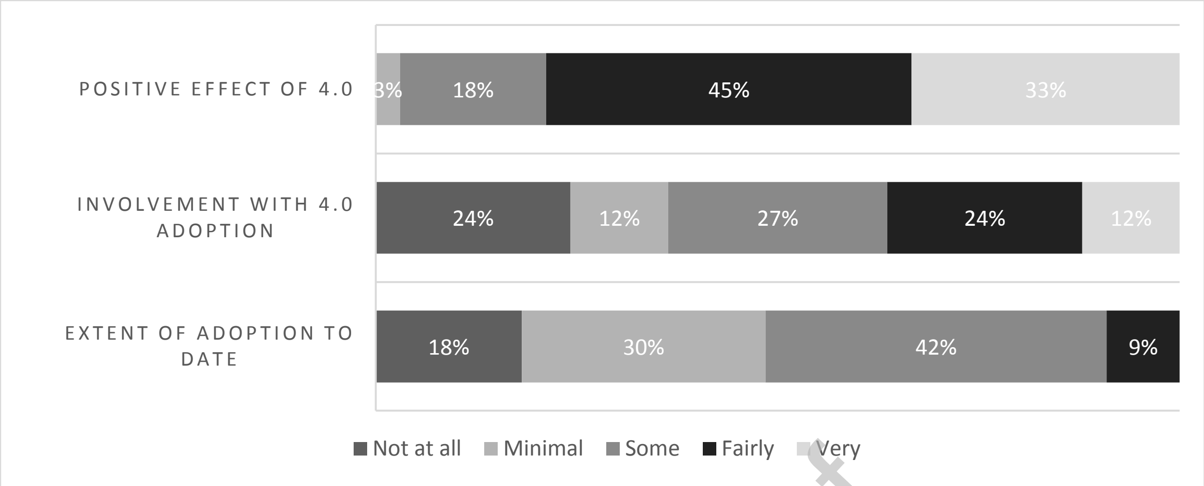

Figure 3 - Rated effect, involvement and current adoption of 4.0, n=33

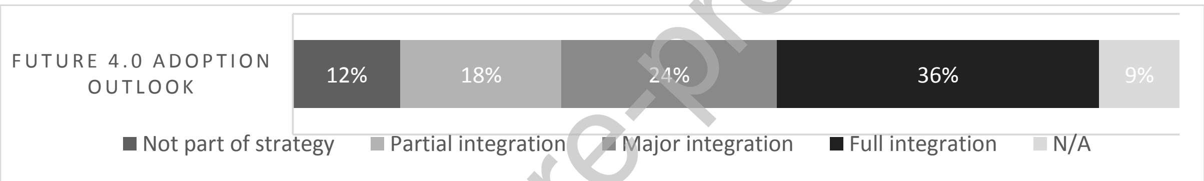

Figure 4 - Rated 4.0 adoption outlook, n=33

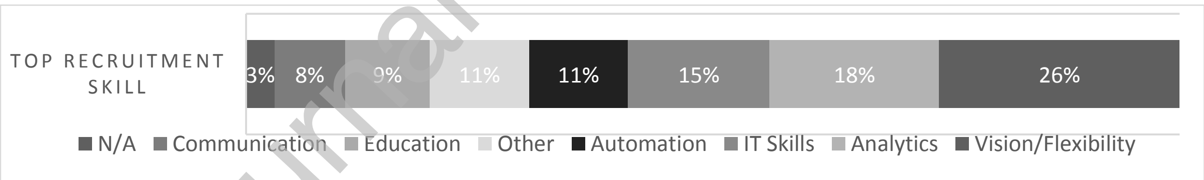

Figure 5 - Skills considered upon recruitment, n=66

Rapid advances in technological development was identified as the single most significant movement influencing the adoption of 4.0 across industry activities:

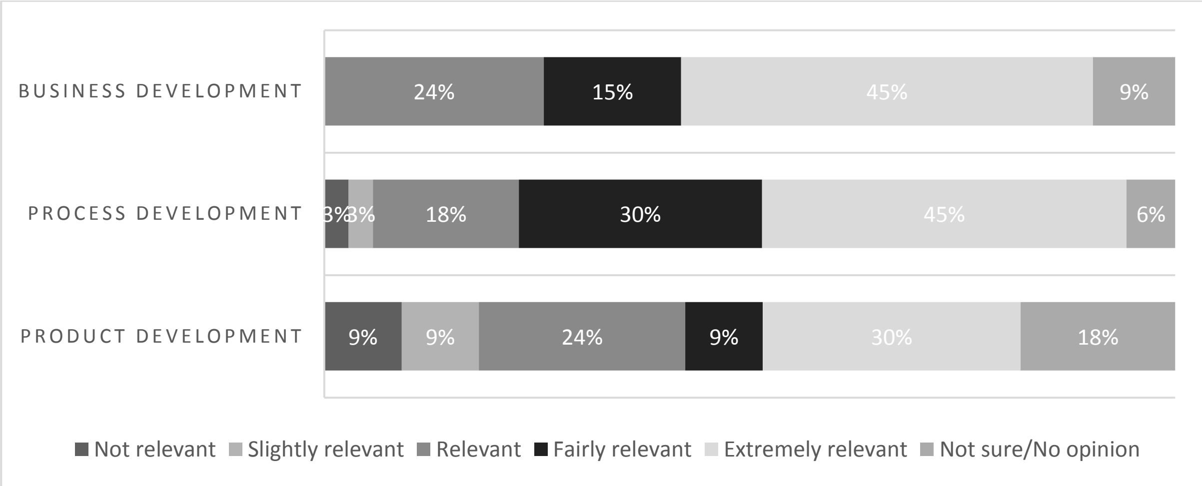

Figure 6 - Rated relevance of 4.0 in indicated areas, n=33

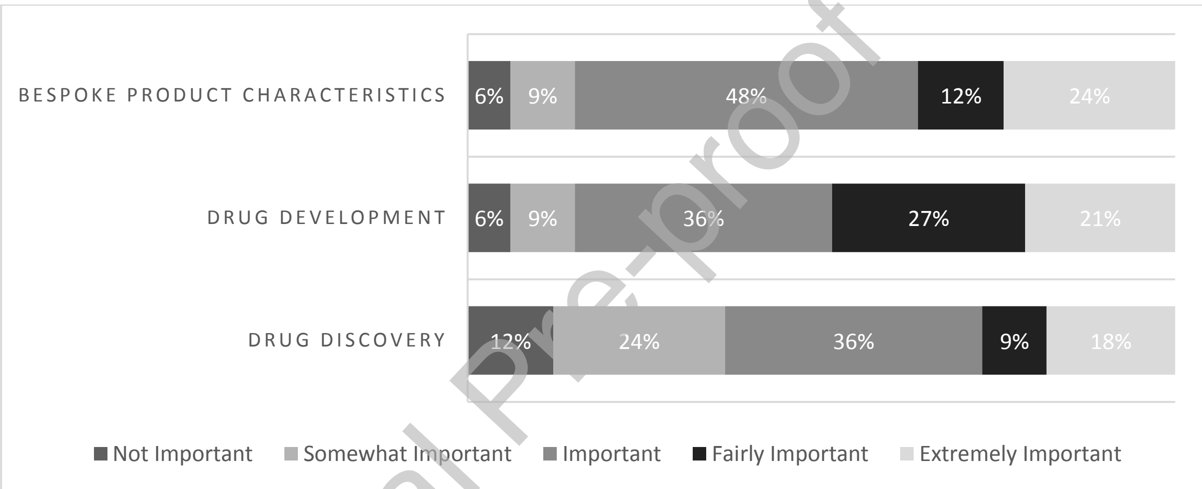

Figure 7 - Rated effects of 4.0 in indicated areas, n=33

Although only 42% of the respondents indicated knowledge of 4.0, the majority of those (70%) identified as Vice-President, Director or Manager. Likewise, when departments within the company were examined, it was found that the bulk of respondents which indicated a knowledge of 4.0 identified with either the Automation or Engineering department. This is in keeping with the general 4.0 trend of technical roles being more involved with its implementation and therefore more knowledgeable about 4.0. A similar trend was seen with regards to experience level – respondents with more than 8 years of experience were more likely to have knowledge of 4.0, with 82% of the responses. This indicates both the lack of a younger workforce presence in higher management positions and the lack of 4.0 knowledge among younger respondents. Research by [22, 23] notes that knowledge transfer and knowledge-oriented leadership within multinational companies is imperative to ensuring a competitive edge, the survey results indicate that complete knowledge transfer is not being implemented across the multinational companies studied.

3.1. Detailed analysis of data

Over the last few decades, maintenance functions have radically evolved with the growth of technology. According to research by [24], maintenance is defined as a set of activities or tasks used to restore an item to a state in which it can perform its designated functions [25, 26]. The concept of preventive maintenance involves the performance of maintenance activities prior to the failure of equipment [27, 28]. One of the main objectives of preventive maintenance is to reduce the failure rate or failure frequency of the equipment. This strategy contributes to minimising failure costs and machine downtime (production loss), and increasing product quality [29].

IT can play a role at all levels of manufacturing operations and is becoming especially evident within Manufacturing Operations Management (MOM) level. Research by [30] suggests that Manufacturing Execution Systems (MES) aggregates a number of the technologies deployed at the MOM level. MES as a technology has been successfully deployed within the pharmaceutical industry since the Food and Drug Administration (FDA) decreed the final 21 Part 11 regulations on 21 March 1997. These regulations provided criteria for acceptance by the FDA, under certain circumstances, of electronic records, electronic signatures and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. Over 16 years on and the technology associated with MES has matured and is fast becoming a recognised best practice across all pharma and life science regulated industries. This is borne out by the fact that most green-field manufacturing sites are starting with an MES in place, in effect paperless manufacturing from day one.

The first steps in an Analytical Quality-by-Design (AQbD) method development include understanding the analysis needs (e.g., purpose, specificity, sensitivity, cycle time, on-line/off-line, qualitative/quantitative, accuracy, precision) and selection of the technique (which is at the receiving lab) that will meet these criteria. One set of analytical tools applied during the development and scale-up of drug substances and dosage forms include in-situ analytics, chemometrics and modelling (i.e., Process Analytical Technology (PAT) tools [31]. Many on-line tools are routinely applied to monitor, measure or control processes. Commonly used PAT tools that are well-integrated and routinely used in manufacturing include thermocouples and pressure sensors.

The use of AR on manufacturing processes regarding to simulation, assistance and guidance has been proven to be an efficient technology helping on problems [32]. AR technology increases operator reality sensitivity by making use of artificial information about the environment, where the real world is fulfilled by its objects [33, 34]. As long as it interacts with human senses, AR can make use of any kind of hardware [35]. Using AR can help on closing some gaps, e.g., between product development and manufacturing operation, due to the ability to reproduce and reuse digital information and knowledge at the same time that supports assembly operations [32].

Extensive amounts of generated data from different types, can come from interconnected heterogeneous objects [36]. This structured, semi-structured and unstructured data can describe Big Data. Systematic guidance can be provided by Big Data for related production activities within the entire product lifecycle [37], achieving cost-efficient running of the process [38], and help managers with decision-making or to solve problems related to operations [37]. The use of Big Data provides a business advantage through the opportunity of generating added value according to [39].

Research by [40] defined Cybersecurity as a new term on a high level of information security, and through the word “cyber” it spreads to apply also on industrial environments and IoT. Cloud computing is an alternative technology for companies who intend to invest in IT outsourcing resources [41]. The adoption of cloud computing has several advantages related to cost reduction according to [39], e.g., the direct and indirect costs on the removal of IT infrastructure in the organisation, the resource rationalisation service by the dynamically scalable users consuming only the computing resources they actually use or portability when using any type of device connected to the internet such as mobile phones or tablets accessing from any world location.

The relevance of 4.0 technologies is therefore becoming even more evident. Given this information, the data is invaluable in providing insight to both academia and industry with regards to the integration of 4.0 technologies. The data set was analysed using Fischer’s Least Significant Difference

(LSD) in StatSoft Statistica. This analysis yielded some statistically significant relationships within the data which are explored here.

3.1.1 Top six 4.0 elements currently operating in companies

The manufacturing industry – be it pharmaceutical, biopharmaceutical or medical devices – strategically wishes to position itself at the leading edge of technologies. Many of these corporations have already implemented aspects of 4.0 into their facilities. Figure 8 provides a clear visual indicator of the projects, which already form an integral part of manufacturing processes. 147 responses identified Preventive maintenance, Manufacturing execution systems, Production line automation, Data mining, Cloud storage & Cybersecurity, Augmented/assisted/virtual reality and Process analytical technology as the top six 4.0 elements currently operating in companies. These six elements presented a combined total of 61%.

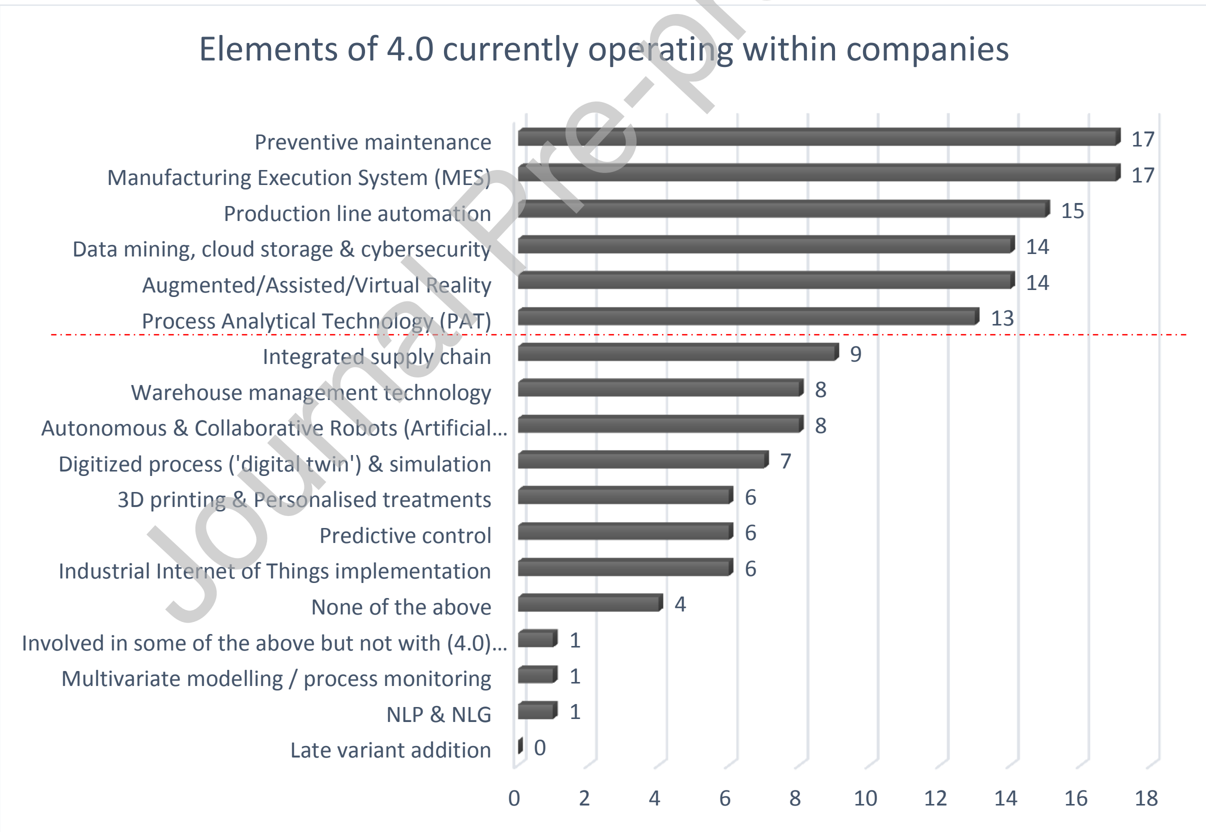

Figure 8 - Top six 4.0 elements currently operating in companies, top elements demarcated, n=147

3.1.2 Main areas of focus & planned future projects

Modern industry faces a myriad of technological options when developing or enhancing processes. It is highly relevant to contextualise these options, what is a high priority and why might that be the case. Figure 9 provides an indicator of the direction industry might take when adopting 4.0. 179 responses identified optimising processes (13%), monitoring plant performance (12%), ensuring regulatory compliance (12%) and minimising downtime (11%) as the top four main areas of focus for industry 4.0. These four areas presented a combined total of 48.6%.

Figure 10 provides a clear visual indicator of the preferences with regards to future projects to be implemented. 263 responses identified Preventive maintenance (7.6%), Cloud data storage (6.8%), Manufacturing execution systems (6.5%), Process analytical technology (6.1%), and Continuous flow manufacturing (6.1%) as the top five planned 4.0 projects across industry. These five projects presented a combined total of 33%.

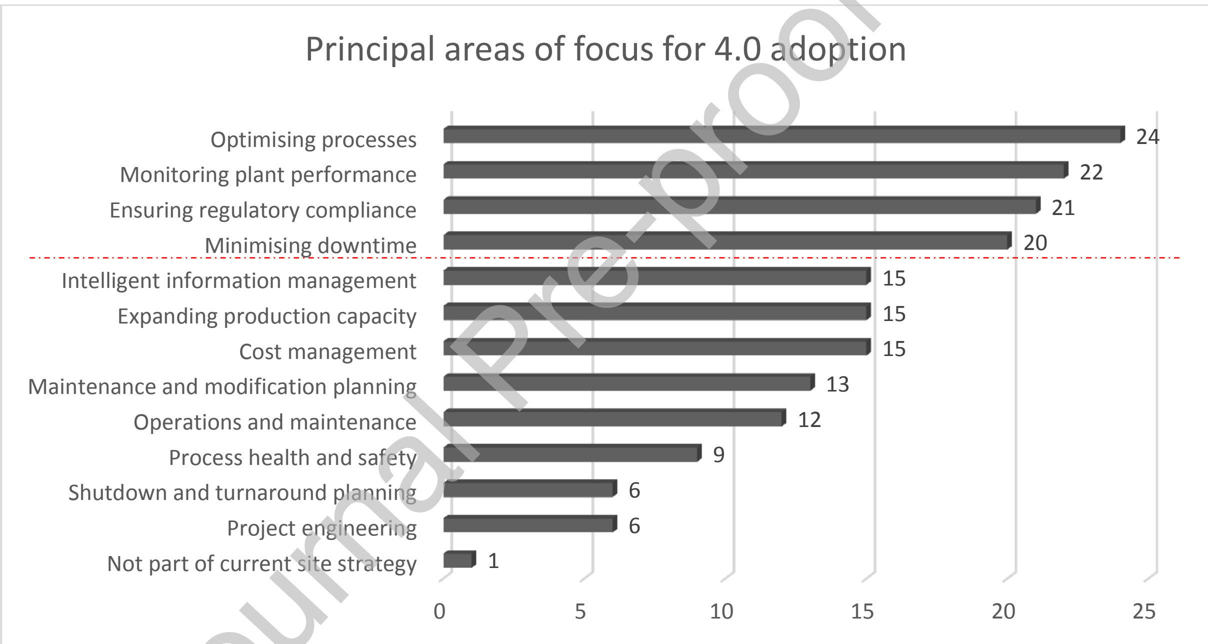

Figure 9 -Principal areas of 4.0 focus, top areas demarcated, n=179

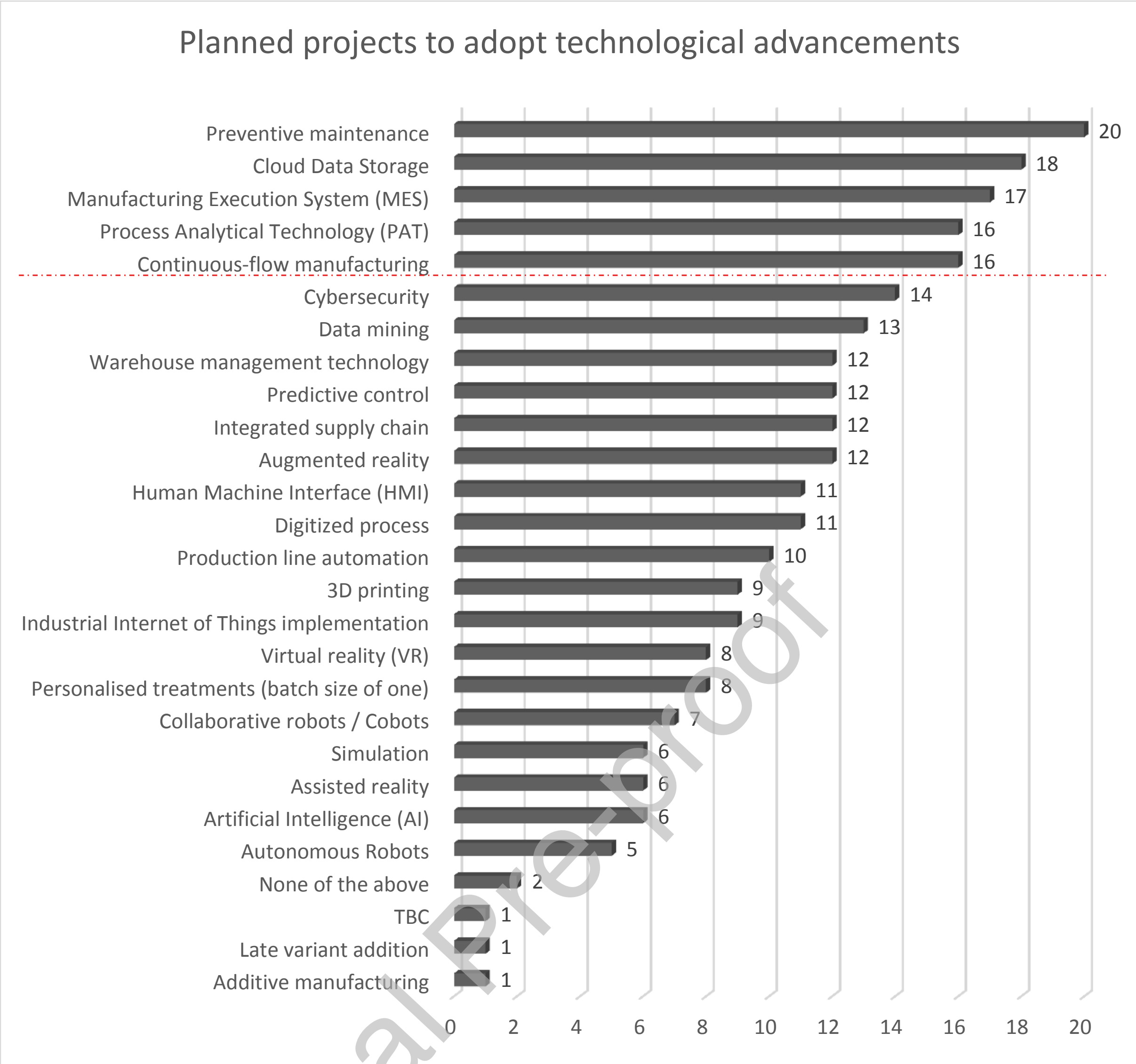

Figure 10 - Planned future projects, top projects demarcated, n=263

3.1.3 5 year goals and type of company significance

Statistical analysis of the data using Fischer LSD detects a significant difference between Medical Devices & Consultancy versus Biopharmaceutical & other types of biomanufacturing.

The p-value in Table 2, part a indicates there is a 96% chance that respondents working in the Medical Devices and Consultancy industries specify that the companies they work for have significantly different 5-year goals than those in the Biopharmaceutical industry and other industries.

3.1.4 5 year goals and type of manufacturing significance

Further analysis of the data using Fischer LSD identifies a significant difference between Complete Manufacturing Facility (consisting of both upstream and downstream manufacturing facilities) &

Medical Device manufacturing facility versus Secondary/Downstream & Consultancy/Design with respect to 5-year goals for companies and type of manufacturing.

The p-value in Table 2, part b indicates there is a 95% chance that respondents from the Complete Manufacturing Facilities and Medical Device manufacturing facility specify that the companies they work for have a significantly different 5-year goal than those in the Secondary/Downstream manufacturing and Consultancy/Design facilities.

3.1.5 5 year goals and role within company significance

Employment role is important with Fischer LSD detecting a significant difference between manager, director & vice-president versus other roles (other roles may consist of technical and validation roles) with respect to the 5-year goals for companies.

The p-value in Table 2, part c indicates there is a 99% chance that respondents who identified as managers, directors and vice-presidents specify that the companies they work for have a significantly different 5-year goal than those in roles associated with the other category.

3.1.6 Continuous-flow manufacturing and primary department significance

In the case of the importance of continuous-flow manufacturing and the respondent's primary department, statistical analysis of the data using Fischer LSD detects a significant difference between process development and the remaining groups.

The p-value in Table 2, part d indicates there is a 99% chance that respondents who identified their primary department as Process Development rated Continuous-flow Manufacturing as more important than respondents who identified their primary department as being one other than Process Development did.

3.1.7 Continuous-flow manufacturing and level of experience significance

With respect to the importance of continuous-flow manufacturing importance and the respondent's experience level, statistical analysis of the data using Fischer LSD detects a significant difference between those with 8-15 years of experience versus the remaining groups.

The p-value in Table 2, part e indicates there is a 99% chance that respondents who identified their experience level as being between 8 and 15 years of experience rated continuous-flow manufacturing as more important than respondents who identified their experience level as being one other 8 to 15 years of experience.

3.1.8 MES & HMI and type of manufacturing significance

When considering to adoption of Manufacturing Execution System (MES) & Human Machine Interface (HMI) and type of manufacturing, statistical analysis of the data using Fischer LSD detects a significant difference between Secondary/Downstream, Complete manufacturing and Medical Device components facilities versus Other types of manufacturing. Other types of manufacturing may consist of Infant Nutrition and Brewing industries.

The p-value in Table 2, part f indicates there is a 97% chance that respondents who identified as Other types of manufacturing were not as well aware of Manufacturing Execution System (MES) & Human Machine Interface (HMI) as respondents from Secondary/Downstream, Complete manufacturing and Medical Device components facilities.

3.1.9 Awareness of 4.0 significance

The awareness of 4.0 within a firm's management shows there are significant differences with respect to primary department and role within company. The p-value in Table 2, part g indicates there is a 96% chance that respondents that identified their primary department as Automation, Operations or Other departments are much more likely to have an awareness of 4.0 than respondents who work in Engineering, Quality, Production, Process Development, Research and Development and Environmental, Health & Safety departments. All respondents who identified as Environmental, Health & Safety indicated no knowledge of 4.0. The department listed as other includes Operational Excellence, Maintenance and Technical Operations. The p-value in Table 2, part g indicates there is a 98% chance that respondents that identified their role within the company as either Vice-President or Director are aware of 4.0. Of particular significance is Vice-President, with all respondents having indicated awareness of 4.0. Similarly, Directors had equally high awareness of 4.0. On the other hand, Scientists and Operators respectively, all stated having no awareness of 4.0.

Univariate Tests of Significance for specified parameter. Sigma-restricted parameterisation Effective hypothesis decomposition		
a. 5 year goals and type of company significance		
Parameter	**Category**	**p**
Type of company	Medical Devices & Consulting	0.036564
b. 5 year goals and type of manufacturing significance		
Parameter	**Category**	**p**
Type of manufacturing	Complete Manufacturing Facilities and Medical Device manufacturing facility	0.047375
c. 5 year goals and role within company significance		
Parameter	**Category**	**p**
Role within company	Managers, Directors and Vice-Presidents	0.005092
d. Continuous-flow manufacturing and primary department significance		
Parameter	**Category**	**p**
Primary department	Process Development	0.006141
e. Continuous-flow manufacturing and level of experience significance		
Parameter	**Category**	**p**
Level of experience	Between 8 and 15 years of experience	0.008678
f. MES & HMI and type of manufacturing significance		
Parameter	**Category**	**p**
Type of manufacturing	Other	0.033555
g. Awareness of 4.0 significance		

Parameter	**Category**	**p**
Primary department	Automation, Operations or Other	0.041755
Role within company	Vice-President or Director	0.017644

Table 2 - Fisher LSD p-value significance study

The Fisher LSD, provides definitive evidence that there are statistically significant relationships within the survey responses. Of particular significance, there is a 98% chance that respondents who identified their role within the company as either Vice-President or Director are aware of 4.0. Of those that identified as Vice-President, all respondents indicated awareness of 4.0. Similarly, there is a 99% chance that respondents who identified as managers, directors and vice-presidents specify that the companies they work for have a significantly different 5-year goal than those who were identified as the other category. This is in keeping with the 96% chance that respondents working in the Medical Devices and Consultancy industries specify that the companies they work for have significantly different 5 year goals than those in the Biopharmaceutical industry and other industries. This may be due to management knowledge sharing as outlined by [22, 23] in their research.

4. Conclusions

The aim of this research was to study the Irish manufacturing microcosm – as a representative sample of the global manufacturing world – and to deduce the following:

- The current level of 4.0 adoption
- Planned pathway for the future
- Future projects to implement technological advancements

Although only 42% of the respondents indicated knowledge of 4.0, the majority of those (70%) identified as Vice-President, Director or Manager. Likewise, when departments within the company were examined, it was found that the bulk of respondents which indicated a knowledge of 4.0 identified with either the Automation or Engineering department. This is in keeping with the general 4.0 trend of technical roles being more involved with its implementation and therefore more knowledgeable about 4.0. A similar trend was seen with regards to experience level – respondents with more than 8 years of experience were more likely to have knowledge of 4.0, with 82% of the responses. This movement indicates both the lack of a younger workforce presence in higher management positions and the lack of 4.0 knowledge among younger respondents.

Delving into deeper analysis of the data using Fisher LSD, several findings were of note. Of particular significance, there is a 98% chance that respondents who identified their role within the company as either Vice-President or Director are aware of 4.0. Of those that identified as Vice-President, all respondents indicated awareness of 4.0. Similarly, there is a 99% chance that respondents who identified as higher management specify that the companies they work for have a significantly different 5-year goal than those who were identified as the other category. Research by [22, 23] notes that knowledge transfer and knowledge-oriented leadership within multinational companies is imperative to ensuring a competitive edge, the survey results indicate that complete knowledge transfer is not being implemented across the multinational companies studied.

It was found that there is a 96% chance that respondents that identified their primary department as Automation, Operations or Other departments are much more likely to have an awareness of 4.0. This may be a phenomenon of silo mentality, commonly found within industry. Also interestingly, it was found that a large amount of represented companies are currently involved in implementing 4.0 either partially, majorly or fully (at 64%) and 40% indicated their companies aimed to have 4.0 fully integrated into the facility in 5 years' time. 97% of respondents which indicated knowledge of 4.0 also considered 4.0 beneficial to industry.

It is expected that the information generated by this survey and accompanying research can be used to determine a suitable pathway for advancement towards a more technologically advanced manufacturing future. The information can be used to deduce the management and technological strategy and direction that industry may take. This is of interest to business corporations, regulatory bodies, universities and professional institutions working closely with industry.

While 4.0 is increasingly being explored by many researchers, it is clear an information deficit still exists as noted by [42]. 4.0 is still in its infancy and to make it a reality, several challenges and gaps must be addressed. The roadmap for the 4.0 execution is still not fully clear for either industry or academia [43]. In order to add to the academic knowledge pool, further research must be undertaken in the field of Pharma 4.0.

Of the respondents that indicated knowledge of 4.0, 64% are currently involved in implementing 4.0 either partially, majorly or fully in their facilities. This is in keeping with the current level of implementation across the manufacturing section in Ireland – as the consumer preferences and market outlook is changing, a large percentage of corporations are looking to keep up with demand and adjust their manufacturing in order to appeal to the modern consumer. Smart factories and smart products are the principal goal, and by adopting technological advancements in their facilities, corporations hope to keep their competitive edge.

The major finding of this work is the identification of a significant disconnect in knowledge based on seniority, function and industry. Thus while the implementation of 4.0 is playing an increasingly significant role in the modernisation of the Pharmaceutical and Biopharmaceutical industries, challenges remain with respect to the holistic fusion of 4.0 into the culture of organisations.

Nomenclature

API – Active Pharmaceutical Ingredient

BPCI – BioPharma Chemical Ireland

CAGR – Compound Annual Growth Rate

IChemE – Institution of Chemical Engineers

IDA – Industrial Development Authority

IMDA – Irish Medtech Association

IoT – Internet of Things

ISA – International Society of Automation

ISPE – International Society for Pharmaceutical Engineering

LSD – Least Significant Difference

MES – Manufacturing Execution System

MOM – Manufacturing Operations Management

PAT – Process Analytical Technology

R&D – Research and Development

Declaration of Competing Interest

None

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