The Technological Readiness of Pharmaceutical Companies in Ireland facing Pharma 4.0

By

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LIST OF ABBREVIATIONS

ACHATEC: combination of academia and technology.

AI: Artificial Intelligence.

API: Active pharmaceutical ingredient.

EMEA: European Medicines Agency

HPC: High performance computing

HPRA: Health Product regulatory Authority

IIOT: Industrial internet of things

IOT: Internet of things.

ISPE International Society for Pharmaceutical Engineering

IT Information Technology.

IT: Information Technology.

NAS: New Active substances.

PM: precision medicine.

R&D: Research and development.

SMEs: Small and medium-sized enterprises

ABSTRACT

The Technological Readiness of Pharmaceutical Companies in Ireland facing Pharma 4.0

Karla Iveth Rodriguez Lagos

The aim of this research was to measure the technological readiness of pharmaceutical companies in Ireland facing Pharma 4.0. Also, describe the triggers and challenges in adhering to the operational model implementation. Through the application of surveys to employees belonging to the pharmaceutical industry workforce, valuable data could be obtained, which was quantified. Using digital maturity measurement instruments was possible to locate the Irish pharmaceutical industry is in the visibility stage which represents a basic level of Pharma 4.0 implementation. Motivated by the increase in its production, but challenged by the monetary and logistical implications of acquiring new technologies. The significance of this study is that it allows obtaining a general description of the level of presence of Pharma 4.0 in the entire pharmaceutical industry. Allowing to show the strength and weaknesses in the capabilities currently present in the industry.

INTRODUCTION

Medical treatments have evolved over time. From formulations based on herbal compounds to nowadays products with complex formulations. In this way, more robust processes is required. This evolution has been motivated by variables that, interacting together, result in an eminent demand for innovation. Emergence of New diseases, fluctuations in the economy, market expansion, new technologies, are some of these variables. The latter has become the trigger that is generating the most impact in the drug production industry. The ability to access new technologies has led companies to seek strategies to adapt them into their process. Furthermore, be able to offer responses to the demands generated by the environment.

The pharmaceutical industry has a very complex nature due to the factors involved in its development. On one hand, they face a social responsibility to generate quality treatments that improve people's quality of life. And on the other hand, the fact that they need to remain profitable in order to continue in the industry. In the end, the pharmaceutical industry has to always be in search of balancing both variables. However, it is not an easy task, since the development of a single drug demands huge amounts of money, long periods of time, and is a very risky path. Besides, just a few drugs that start their research phase go on the market. We cannot forget the pressure and methodology that regulatory systems add to the pharmaceutical industry to ensure that its products are safe for consumption. Which adds even more complexity to the Industry.

Therefore, the need to meet the demands generated by the industry without losing the quality and safety of the drugs is a reality. For this reason, the Pharma 4.0 operation model has emerged. This operation model is rooted in the principles of Industry 4.0. And offers to transform current manufacturing systems into more digitized ones. Starting from automated processes, but adding digital technology. In this way, by joining these two areas, it will be possible to have more transparent and agile processes capable of use data, transform it into information and generate immediate changes. As a result, production systems are capable of predicting future scenarios and have the possibility of evolving and adapt more quickly.

Digital technology is revolutionizing the manufacturing industry. The implementation of these new operating models has ceased to be a trend to become a necessity. For this reason, the

pharmaceutical industry in Ireland has proven to be very solid over time and with the ability to evolve in a short period of time. It is considered the perfect scenario for the implementation of this type of model. This being the motivation for develop this research. The aim of this study is to identify the current Pharma 4.0 readiness level of the Irish pharmaceutical industry. As well as, identify its motivators and the challenges they face in the adaptation process. It is not possible to achieve an evolution without first knowing your current condition. It is necessary to be aware of the company's strengths and weaknesses to create the best strategy that will lead to a successful evolution. For this reason, this research offers an overview of the current Pharma 4.0 presence in the Irish pharmaceutical Industry. Which represents a valuable contribution for pharmaceutical companies in recognizing the overall readiness in the whole industry. To the best of our knowledge, no study was identified that measured the current presence of Pharma 4.0 in Irish pharmaceutical companies.

The Dissertation consists of 5 chapters. Chapter 1 presents the review of the literature, in which the pharmaceutical industry globally and in Ireland is presented as well as explains in detail the concepts Phar 4, .0, and industry 4.0 with complementary ones. Later, chapter 2 introduces the methodology used during the research as well as the data collection process and the way in which they were quantified. Further chapter 3 compiles the findings obtained from the investigation, subsequently, Chapter 4 provides the analysis of the results and their implications. Finally, chapter 5 comprises the conclusions and recommendations resulting from the investigation.

CHAPTER 1

1. LITERATURE REVIEW

1.1 Pharmaceutical Industry

The pharmaceutical industry is responsible to provide medical treatment for human and animal used by discovering, manufacturing, and commercializing pharmaceuticals drugs. Particular dominated by a small number of huge multinational companies, collectively known as Big-Pharma. These companies, have dominated the market for a long time. Maintaining robust R&D programs in order to be the first to offer innovative products to the market. Big Pharma companies cover 40% of the market in financial terms, but they represent a very small percentage when refers to the entire industry. The rest of the industry is represented by generic companies which actually produce most of the drugs sold in the market (Taylor, 2016).

Historically, it was in the 20th century when the greatest advances within the industry started to take place. The second civil war can be considered as one of the main factors that triggered companies to become research-based organisations. Since, drugs such as antibiotics and pain relievers were required substantially during this period (Taylor, 2016). From this point on, the growth of the pharmaceutical industry accelerated, generating an increase in companies interested in this market.

Companies began to direct their business model to R&D, therefore the companies that dominated the market were those that had the possibility to bring new drugs to the market. The development of new drugs is a long process, extremely expensive, risky and with many regulations that must be accomplished. In order to reach the commercialization stage and achieve the monetary return to the company, a prior billion investment is necessary. For this reason, when a new drug is release to market, there are legal regulations that ensure exclusive rights to sell it. Through patents it is ensured that these research-based companies remain profitable protecting the exclusivity of the drug for a period of time, around 10 to 12 years. After this period of time these drugs can be replicated by other companies and commercial at lower prices. These companies called generic companies as mentioned above are the ones that generate the highest sales in the market.

It is a very disproportionate situation, research-based companies focus their business model on the constant strengthening of their R&D programs. They invest large amounts of money and time to bring new drugs to market. These costs can vary depending on the area of research and the type of technology used during development stage, which is the phase that dominates the costs. The

average cost of bringing a new drug to market is $ 1.3 billion, data obtained from a study that analysed 63 new therapeutic drugs approved by the FDA (Wouters et al., 2020).

On the other hand, generic companies avoid these long research processes and focus their business model on replicating drugs that are already accepted in the market. By avoiding the R&D process, the costs of bringing drugs to market that they confront are substantially reduced. Generating the ability to offer medicines with the same composition, but at a lower commercial price. For this reason, in general, the majority of the population views large pharmaceutical companies as representatives of the pharmaceutical industry, but the reality is that most sales are generated in generic companies that are awaiting the expiration of patents to increase their income.

In recent years the pharmaceutical industry is confronting several changes generated by due to the emergence of new technological, scientific and market opportunities (Malerba and Orsenigo, 2015). The research area specifically is currently going through an important crisis. The blockbuster drug, which is the name given to drugs that manage to generate annual sells over $ 1 billion (Li, 2014), has represented a long-term competitive advantage for pharmaceutical companies. It was in 1970 when GSK launched its first Blockbuster drug on the market and since then this theory has been maintained. However, technological advancements, are provided the opportunity to better understand diseases and thus changing the way to combat them (Seyhan and Carini, 2019). As a result, health systems are demanding more personalized treatments, currently known as personalized medicine. European Commission, defines this term as a medical model that aims to use the characteristics of individuals to offer tailor-made treatments. At the same time, it indicates that it is a model for the evolution of medicine that is still under development since many changes have to be implemented for its successful development.

1.2 Pharmaceutical Industry in the world

The pharmaceutical industry is undoubtedly a main pillar of the global economy. Social factors such as new diseases, demographic changes, increase in world population, new markets discovery, are factors that have led the pharmaceutical industry to grow exponentially. In fact, in Europe in 2019 € 37.5 billion were invested in R&D programs (Efpia, 2020). Globally, the 3 largest

representatives of new drugs launches are the United States, Europe, and Japan, with a representation during the 2014-2019 period of 62.3%, 18.4%, and 6.5% respectively.

According to IQVIA Institute for Human Data Science, the global expenses generated for the production of medicines in the year 2018 reached $ 1.2 trillion, up from $ 1.1 trillion in 2017 with an annual growth of 4-5%. Growth for subsequent years is projected to be primarily focused on the launch of innovative products. (Institute for Human Data Science, 2019).

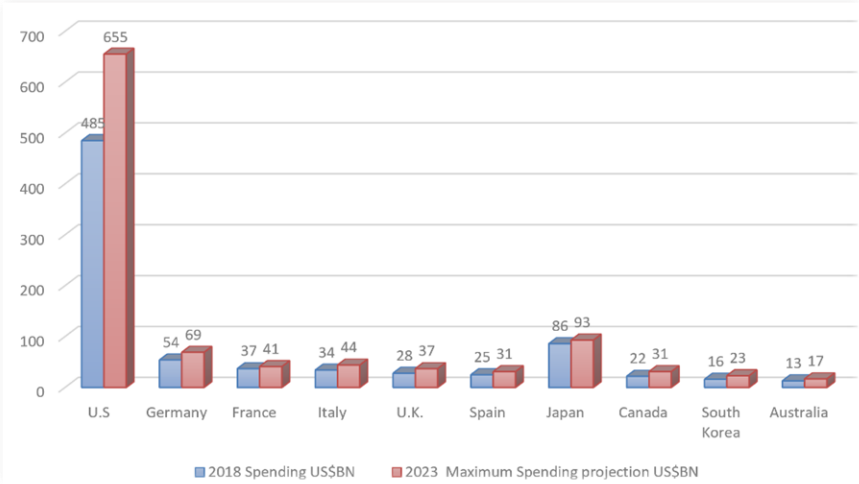

Figure 1. Global Spending and Maximum spending projection

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Source: (Institute for Human Data Science, 2019).

Figure 1 describes the market sizes in trillions of dollars of the countries with the highest representation in the pharmaceutical industry. As well as the maximum projection for the year 2023. The United States is in first place with an investment in the pharmaceutical market of $ 485 trillion dollars and a projection for the year 2023 of $ 655 trillion. One of the reasons why the United States offers a greater worldwide presence is because a large number of companies that belong to big pharma are originally from this country. Therefore, United States has companies with solid experience with access to innovative technologies that allow these companies to continue performing R&D programs, and maintain a presence in the market. Also, it is a country that has its own regulatory system called the FDA. It is also noteworthy that all the countries in

Figure 1 reflect growth in their projections for 2023. The pharmaceutical industry is constantly expanding encompassing new markets that are called emerging markets. Countries such as China, Brazil, India and Russia, are clear representations of these markets. *Figure 2* illustrates a growth projection of 5-10% of these markets by 2023.

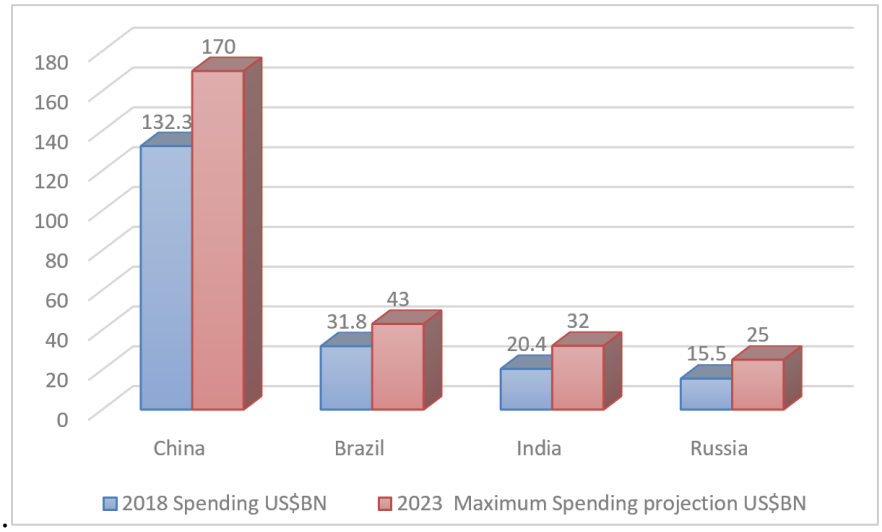

Figure 2. Global Spending and Maximum spending projection in emerging Markets

Source: (Institute for Human Data Science, 2019).

1.3 Global Trends

As stated above, the pharmaceutical industry is facing many significant changes and challenges now more than ever. Considering that global economic uncertainty, expiring patents and major healthcare costs, the industry reflects being in a turbulent stage. Therefore, the industry tries to adapt and change course in a direction that meets the environment's demands. As a result, a number of emerging trends are taking place. The ones that are considered to be transforming the industry to a greater extent will be discussed below.

1.3.1 R&D-fluctuations:

The cost of launching a new drug, as mentioned previously reaches more than $1 billion, and takes around 12 years to be available on the market. On average, only one or two of 10,000 substances that start their research stage is marketed. Research-based pharma companies are opting as a

strategic, the increase in investment in their R&D programs in order to expand their portfolio and continue generating profit. The average growth in annual spending generated R&D programs during 20015-2019 in Europe and the United States was 4% and 11.3% respectively versus 2.7% and 3.2% which was reflected during the period of 2010-2014 (Efpia, 2020). However, it is not a strategy that is reflecting major advances. The number of annual launched drugs has not presented any significant change. In this way, the investment in R&D programs, focused on expanding business areas does not necessarily lead to innovative products.

1.3.2Biotechnology

Globally, there has been an increase in the launch of New active substance (NAS), in the period 2009-2013 an average of NAS launches of 36% was reflected, rising to 46% in the period 20014-2018 and with a projection of increasing to 54% for the year 2023 (Institute for Human Data Science, 2019). In conjunction with this increase in new product launches, they are apparently being focused on biotech, specialty, orphan and oncology products. Biotechnology-based drugs are much more complex and expensive to develop compared to conventional drugs, however, they offer much more effective treatment with the ability to offer much more personalized treatments and cover areas that have not been treated previously. This is why betting on the development of new drugs based on this technology and focused on new areas to explore represents a global trend that is leaving big profits for the companies that are developing it.

1.3.3Precision Medicine

Personalize healthcare has been indicated as the future of healthcare systems. Precision Medicine aims to offer personalized treatment to patients. Additionally, these treatments offer to be more effective and help reduce side effects generated by standard treatments. (Seyhan and Carini, 2019).

What represents an opportunity for the health system, represents a challenge for the pharmaceutical industry. Since, the manufacture of precision medicine demands companies to have specialized production systems. Able to adapt to new drug formulations quickly.

1.3.4 Emerging Markets.

Emerging markets have become a very attractive business for pharmaceutical companies. Although an exact definition is not specify economists define emerging markets as developing countries where investment is expected to generate higher returns despite high risks (Tannoury and Attieh, 2017). Beyond the opportunity to generate higher income, aspects such as the wide availability of a workforce and lower operating costs attract large companies to invest in this market. Allowing them to manufacture drugs at a lower cost, and increase production capacity.

The countries that stand out in this category of emerging markets are the so-called MINTs (Mexico, Indonesia, Nigeria, Turkey) and BRICS (Brazil, Russia, India, China and South Africa). Which, due to their specific economic characteristics, represent an opportunity for investors to generate higher returns. To determine whether or not a country represents an emerging economy does not only depend on the economy itself. Aspects such as large populations, strategic geographic location, skilled labor force and life expectancy are analyzed by investors.

Pharmaceutical companies that want to grow in these markets must implement defined strategies base on each country. Which should be focused on cover the needs that the countries demand. There is a strong trend that in these countries the greatest affection is caused by chronic and infectious diseases.

Therefore, emerging markets is a trend that is growing mainly due to the low operating costs it requires and the large returns it generates, which is very attractive for companies. Although there are risks that have to be borne by companies, the benefits appear to be preponderant.

1.3.5 New Technology implementation

The fluctuating environment in which the pharmaceutical industry finds is pushing companies to adapt their supply chain to a more efficient and faster one. Automated processes are being adopted in most manufacturing stages to meet this demand.

“Today's automation systems are more capable and flexible than ever”(McKinsey, 2017). It is a fact that the presence of automated processes is increasingly found within the industry. Companies

seek to replace repetitive processes that take long time with faster and more efficient ones. And this has been achieved in recent years through the implementation of automated machinery.

Today, even more innovative technologies continue to be adapted to these automated processes to generate even more efficient systems. Machine-learning is a concept that is being managed by manufacturing companies. Is a method that uses data, transforms it into information and then generates automatic changes within the processes. It is a branch of AI that aims to use the data generated in the processes to the maximum. This technology uses the data obtained to fully understand the manufacturing processes and make them transparent, that is, knowing exactly what is happening and to generate immediate changes if necessary. At the same time, data management implies having secure systems capable of storing large amounts of data. Therefore, there is a great tendency to convert the current automated processes to more digital processes where human-machine communication is possible. Allowing to offer voucher services and remain competitive in the market.

Definitely these new trends, and the constant search for innovative treatments is leading pharmaceutical companies to modify their structure and change their traditional business model. In order to evolve to more agile structures and models capable of adapting to the changing demand of the industry. These new approaches have led large pharmaceutical companies to merge with small or medium-sized companies specialized in biotechnology research, which do not have the monetary and infrastructural capacity that large renowned companies already have, so the union of both represents a quite profitable option today.

1.4 Pharmaceutical Industry in Ireland

Ireland's manufacturing sector which includes Pharmaceuticals, chemicals, food, medical devices, and electronics, appears to be very powerful, encompassing 35.5% of the country's economic income and generating more than 200,000 jobs nationwide (DBEI, 2018) . Definitely, for Ireland, the manufacturing area is an area that can be exploited to continue to maintain it as one of the main elements in the country's economy.

Referring to the pharmaceutical industry, Ireland is considered one of the leading countries. Although most of the companies have only had a presence since 1960 (IPHA, 2021). Currently, Ireland is a strong global supplier of pharmaceuticals. Offering a very attractive location for investment to global drug manufacturing companies. Irish pharmaceutical industry has a mix of multinational companies, start-ups, SMEs focused on the manufacture of APIs, as well as a growing number of R&D programs and Clinical trials that form the representation of the pharmaceutical industry within the country. Within these multinational companies are 10 of the most important companies in the pharmaceutical industry worldwide that have made millions in investments, which has led the pharmaceutical market to grow exponentially in recent years. Among them, we can mention Pfizer, Jassen, MSD, Sanofi, Alexion, Allergan, etc.

Initially, the country manufactured API ingredients for export to other countries where the factories manufactured the final product were located. Eventually, these factories settled in the country and this is how the industry initiate to expand. In 2019, the pharmaceutical sector was the sector with the highest representation in the country's exports, comprising 53% of total exports. Represented in € 80 million and with a growth of 8% compared to 2018. Becoming the second country with the highest exports of medicines and medical products in the European continent(DBEI, 2020).

The Irish pharmaceutical industry is also characterized by performed national and international quality standards. Ensuring compliance with The European Medicines Agency (EMA), which covers the European Union (EU) and The Health Products Regulatory Authority (HPRA), which is a local regulatory body. Additionally, the country offers a skilled workforce, accessibility for credits, and competitive tax rates. It is an industry that promises to continue expanding in the country. Since companies are growing and the emergence of new investments as well, investments focused on the development of innovative products. The biopharmaceutical industry in Ireland has invested an approximate capital of $ 8 billion in the development of new facilities in the last 10 years, making it one of the largest investments in Biotech facilities worldwide (IDA, 2021)

However, being considered a leading country in any area is not an easy task, therefore, Ireland has recently had to face difficulties that have led companies to seek to evolve and adapt, such as Brexit and the COVID-19 pandemic. Between Brexit and all the modifications in alliances and exports

with the UK and the entire European Union, Ireland through HPRA has established a working group to prepare the country for this transition and to affect the pharmaceutical market minimally.

The covid-19 pandemic represented a challenge for the global pharmaceutical industry and obviously in Ireland as well. Resulting in the necessity to explore new areas that were not previously explored. Such as telemedicine, which seeks to provide medical attention remotely. At a global level an investment of US $ 148 billion by 2025 is projected for the development of projects related to telemedicine (DBEI, 2020). Furthermore, companies in Ireland are focused on developing vaccines and treatments against this virus. Hence, the next major investment in science is predicted to be focused on COVID-19. IDA, which is an agency that is in charge of monitoring the country's industrial growth, has published a new scheme for the distribution of goods to support R&D programs related to COVID-19, which involves the distribution of 200 million euros for development support for all products related to the virus.

The Irish Pharmaceutical Healthcare association, attributes the rapid development of the pharmaceutical industry to the fact that the country has a culture of support for innovation. What can be sustained with the implementation of Ireland’s Industry 4.0 Strategy 2020-2025 which also includes the pharmaceutical industry.

1.5 Industry 4.0

1.5.1The fourth industrial revolution

In the course of human history four stages took place, stages that have changed the industrial processed, economic and structural systems of society. Each of them reflects specific characteristics and massive changes. Triggered by the emergence of new technologies in the industry, and resulting in what today we know as the industrial revolutions.

The agricultural revolution took place around 1500 and 1700 (Kerridge, 2013). Animal’s domestication is the most representative change that occurred in this stage. Which represented a new technology that shaped the industry for the following years. Together with the human workforce, the approaches to production, communication, and transport were totally modified.

Resulting in production schemes focused on income generation and a more built and urbanized society.

Consequently, the so-called first industrial revolution arose between 1760 and 1840, this phase was triggered by the necessity to construct railways and expand geographically as a society. The workforce that was previously generated by the human-animal union is transformed into mechanical power due to the invention of steam engine technology. By virtue of this new technology, larger-scale production systems were initiated, transportation systems with greater coverage, and communities connected to each other.

In the late 19th, the second industrial revolution emerge, triggered by the need of generating mass production within factories, a fact that was possible due to the invention of electricity. The invention of electricity triggered the discovery of new communication technologies, electronics, new chemicals used in industry, and scientific knowledge began to be recognized as a fundamental element for the development of the industry. (Schwab, 2016). Followed by the third industrial revolution which began in the 1960s. It is also known as the digital revolution, due to the emergence of computer systems, digital technology and the internet. Finally, at the beginning of the century, the fourth industrial revolution began. Bringing new technologies such as cyber-physical systems, sensors, and cutting-edge technologies capable of acquiring and offering data in real-time. In this way, fully automated and interconnected processes capable of making decisions without human intervention is nowadays available. (Schwab, 2016)

Evaluating all industrial revolutions overall, it can be highlighted that all were triggered by specific reasons oriented to expand production, society, and communication. Needs that sought to be covered through the implementation of innovative technologies. Throughout history, humans demonstrate the constant search for evolution and adaptation, taking the elements developed thanks to scientific knowledge and incorporating them for economic and social benefit. Furthermore, the time of emergence between each of the revolutions is shorter and the incorporation of human force is reduced. In other words, the industry evolves more rapidly every day, forcing society to adapt.

1.5.2 Industry 4.0

Industry 4.0 is a term that was used for the first time in Germany in 2011. German government utilised the term within its strategy for the development of digitalisation programs in the manufacturing Industry. Since then it has been adopted around the world (Manzano and Lange, 2018).

The main objective of Industry 4.0 is to implement innovative technology within the manufacturing industry, capable of connecting the physical world with the digital world. This model involved different technologies, which connect machines, facilities, and humans. Additionally, a new approach of control, monitor and make decisions is possible. Thought collection, storage, and analysis of all data generated during the production process. In this way, Industry 4.0 transforms manufacturing processes into more transparent, productive, agile, and with immediate optimization capability. Industry 4.0 aims to connect different facilities at a global level and the ability to access data and even control machines remotely. Bringing to the industry the possibility of geographic expansion and implementing customer demands into processes.

1.5.3 Key Technologies involved

Below is the description of the key technologies implemented to achieve Industry 4.0 manufacturing level:

- Cloud computing: It is defined as the acquisition of computer services capable of providing databases, software and storing and analysing data. Everything through the internet or "Cloud". This technology eliminates paper-based data management. Everything is digital using cloud services with enormous storage capacities. It also offers benefits such as lower operating costs, the ability to quickly adapt if necessary, and the ability to have paperless production systems. (ISPE, 2014).

- Internet of Things (IoT): This concept refers to the ability to connect devices to the internet in order to centralize the information obtained by each of them. In the manufacturing sector,

IIoT generates connections between machinery and infrastructure. In this way, information is available immediately(Chan, 2016). The entire production process is connected, from its planning stage to the delivery of the product. Thus, provide total visibility throughout the process. Allowing, much faster defects detection, avoid future recalls, increase machine performance and the possibility of involving customer requirements in production systems.

- High-performance computing (HPC): Refers to computer systems capable of analyzing a large amount of data that cannot be handled with a standard computer system.

- Machine learning: Systems that use artificial intelligence, that is, computers and equipment previously programmed to imitate the human capacity for analysis and problem solving. The integration of artificial intelligence allows to predict future scenarios using statistical systems and algorithms. Resulting in costs reduction and production capacities increment.

- Cyber security: As described before, Industry 4.0 approach involves systems that manage and store a large amount of data. Therefore, cyber security is completely necessary. Security systems ensure that all stored data is only accessed by authorized personnel, denying access to any agent who pretends to cause any disruption in the system. Cyber security is a fundamental element within Industry 4.0. US$500 billion is the annual cost estimated by companies due to cyber-attacks (Schwab, 2016). In this way, certain companies consider one of the greatest risks of evolving to Industry 4.0 systems. On the other hand, other companies claim that through innovative management and safety strategies the chances of suffering a cyber-attack can be completely avoided.

Industry 4.0 affects the entire value chain within a manufacturing process, it is not only a connection between the data and machines, also human plays a big role within this connection. This includes producers, workers and suppliers. Which brings one of the first concerns that emerged during the implementation of Industry 4.0, the lack of qualified workers (Schwab, 2016). This companies' concern is totally opposed to the idea that commonly states, about industry 4.0. Which is that this approach will lead to an economy with a higher level of unemployment, due to

the reduction of human intervention in the process. However, the demand for personnel is still required but the approach of the skills set is different. Most of the employees who work in production companies as operators are limited to performing repetitive physical tasks. Industry 4.0 demands a skill set based on knowledgeable personnel rather than physical strength. This is an easy task for developed countries since they have a high-quality education system that can cover this demand and any other developing market demand in the future.

The developing countries on the other hand, are normally used by global companies to reduce production costs since for several reasons the labour force is much cheaper compared to developed countries. For global companies, a cheap labour force will already be an important factor, because they have automated systems.

1.6 Maturity Index

A large number of worldwide companies are truly aware of the benefits offered by the implementation of Industry 4.0. Companies that adhere to Industry 4.0 within their strategies transforms to agile companies capable of implementing immediate changes without facing any disruption in their processes. At the same time, it turns into in one of its competitive advantages in the market. However, many others are in the early stages of development or even some do not have a clear path of how to carry out this transformation.

Studies present that in countries such as Germany, Japan and the United States, more than 50% of their companies have the expectation that through Industry 4.0 their level of competitiveness will increase. However, less than 30% have a clear plan that allows them to achieve this objective (Infosys, 2018). In other words, companies are aware of the need for digital transformation generated by the pressure of competitiveness in the market. However, they do not have the knowledge of how to implement it within their companies successfully, so a large number of implementation initiatives are failing. (Schuh et al., 2020). This is regularly because they focus on individual technologies and corporate objectives are not taken into account. Industry 4.0 is not only about the technology, organizational and cultural elements of the company must be considered, and the implementation must be gradual starting with pilot projects that are later carried out on a large scale.

“Industry 4.0 Maturity Index Managing the Digital Transformation of Companies”, project carried out by various research organizations and published by ACHATEC. Is a systematic guide whose objective is to lead companies in their adaptation processes to Industry 4.0. The main objective of this model is to lead manufacturing companies to a successful digital transformation. Affirms that the digital transformation is not only based on the implementation of cutting-edge technology, but that it is a joint effort that involves structural areas of the company. In this way, understand their current business strategy and its four structural areas of, resources, information systems, culture and organizational structure. Which will be described in more detail in 1.7 Pharma 4.0.

The Industry Maturity Index exposes 6 stages (Computerisation, connectivity, visibility, predictive capacity, adaptability). Each one with specific characteristics, which serve to define in what stage of digital maturity the company currently is and what will be the target to achieve. The stages are in staggered order, so the characteristics of a stage must be met if you want to advance to the next. In this way, the maturity index links the 6 stages to the four structural areas to identify their overall digital maturity.

To this end, the six stages are described below:

1. Stage one, Computerisation: Today computerization systems are largely integrated within most companies. And it is basically implemented to reduce time in the development of processes. The main characteristic of this stage is that despite the fact that if Information technology is used for data acquisition, the information systems are isolated within the company. In the manufacturing area, currently most machinery has a digital interface; however, it is still possible to find manually operated machinery. By presenting data acquisition in isolation, it is much more difficult to identify at which stage of the process an error occurs. Organizationally speaking, companies that are in this stage present a traditional hierarchical structure, where management positions generate instructions and any innovation proposal and employees wait and follow directions. Employee-generation communication is carried out through previously established channels.

2. Stage two, Connectivity: At this stage, the isolated systems of technological information cease to be isolated and become systems that connect most of the stages of the production

process. At this stage a great transformation to the digital world is made, however there is no total connection between the physical and digital world. Organizationally speaking, the traditional hierarchical structure remains, open to the implementation of innovative systems focused on continuous development. However, this openness to innovation is not solidified by the lack of resources and strategies that lead to agile processes, therefore, the implementation of changes is a process that takes time.

3. Stage three, Visibility: At this stage a large number of process sensors are implemented, which capture huge amounts of data. This visibility that exists throughout the process is called digital shadow. Unlike the previous stage, here there is a total connection of the processes within the company that can be made and not only connections in certain areas of production. As its name indicates, this stage allows visibility from the beginning to the end of the process, allowing decision-making based on current real data.

   The traditional hierarchical organizational structure is eliminated, instead it focuses on involving all the employees of the company who can contribute elements to a decision making. What generates that employees are more motivated to continue developing their capabilities to continue expanding their knowledge. The cultural approach is continuous improvement that provide faster responses to the customer through innovative processes that can be proposed by any employee.

4. Stage four, Transparency: At this stage the company uses its digital shadow to achieve a full understanding of why something is happening. Technologies capable of analyzing large amounts of data, what is commonly referred to as "Big Data" are implemented to identify root causes that become knowledge base for the selection of complex decisions. Employees have the knowledge capacity to initiate and propose changes and also get involved in their execution.

5. Stage five, Predictive capacity: The simulation of different future scenarios generated based on the digital shadow of the companies takes place in this stage. Allowing the implementation of measures in due time to predict scenarios that cause negative impacts.

The level of confidence of the prediction capacity in a company depends on the quality of development of its digital shadow plus the implementation of programs capable of big data analysis.

Employees have the ability to take quick action based on the predictive information provided when required. The organizational structure of companies is focused on rapid adaptation, so that employees are open to assigning new tasks and rotating them.

6. Stage six, Adaptability: Because it is the final stage, Industry 4.0 Maturity is fully reached, therefore decision-making is carried out by AI programs. They are processes capable of collecting data, analysing it and at the same time making a decision that leads to the best of benefits. As a result, companies work with processes that can be fully adaptable to new market demands. Adaptability demands adaptable employees who are constantly developing skills that contribute to the process and that lead to new ones. The organizational system is characterized by being flexible and change is more of a rule than an option.

Below in Table 1 is a summary of the implications of each stage based on each structural area.

	RESOURCES	INFORMATION SYSTEMS	CULTURE	ORGANISATIONAL STRUCTURE
Computerisation	The processes integrate computerized systems, however not all equipment has a digital interface	Isolated information systems	Focus on Fulfilment of company mission and vision following already stablish processes.	Traditional hierarchical structure, communication with employees is through previously established channels
Connectivity	The processes offer a wide digital interface, which allows stages of the manufacturing process to be connected and offer data in real time.	Most of the stages of the production process are connected	Open to the implementation of innovative systems focused on continuous development.	Traditional hierarchical structure, here is an organizational culture open to change and innovation. However, due to lack of resources, these changes cannot always be implemented.
Visibility	The processes offer a wide digital interface due to sensors that monitor the critical parameters throughout the process, data that is stored and available at all times for quick decision-making.	Total connection of the processes within the company	Continuous improvement that provides faster responses to the customer through innovative processes	Communication is not hierarchical, so employees are involved in discussions of improvements in innovation and change processes.

Transparency	The processes offer complex digital interfaces, allowing a broad understanding of the process and quick identification of the roots of problems.	Technologies capable of analysing large amounts of data. Big Data	Focused on rapid adaptation, understanding errors and creating new process to avoid them in the future.	Communication is clear and fluid and employees have the power to generate changes and innovations.
Predictive capacity	The processes offer complex digital interfaces, which have the ability to predict future problems and solve them automatically without human intervention.	Ability to predict future scenarios through data analysis.	Openness to change and innovation	Agile project management characteristics, where it focuses on the continuous training of the employee for the application of competencies
Adaptability	The processes are fully automated allowing the ability to adapt quickly if required.	Total data control throughout the process, providing the ability to adapt the process at all times.	Focuses on fostering innovative processes, change is a Must.	There is an organizational structure focused on being Adaptable, with a multidimensional system of goals, employees are constantly reviewed to be able to be adjusted if necessary.

Table 1.Maturity Index. Summary of Stages and Structural Areas

Source: (Schuh et al., 2020)

Industry 4.0 not only encompasses a transformation in its technology and communication systems. Change requires a transformation of the company culture. It is necessary to generate a change in the way that companies currently think and become aware that data management does not achieve its maximum effectiveness if it is only used to perform analysis in specific areas of the process. Data has the ability to provide valuable information and create connections that greatly increase the productivity of the business as a whole. Each of the characteristics of each stage is a reflection of this, it is not possible to evolve to stage 6 and achieve the total approach of Industry 4.0 without going through each of the stages and developing the capabilities in each structural area of the company.

1.7 Pharma 4.0

The fourth industrial revolution has already intervened in the pharmaceutical industry, unleashing the concept of Pharma 4.0. It was introduced in 2017 by the International Society for Pharmaceutical Engineering (ISPE). Pharma 4.0 is a model that aims to apply all industry 4.0 principles strategies into manufacturing processes within pharmaceutical companies, in order to

generate greater productivity, flexibility, compliance with standards, connectivity and faster decision-making processes(ISPE, 2021).

The main objective of Pharma 4.0 is to transform current pharmaceutical manufacturing processes into much faster and more efficient ones. That is, increase your production and eliminate wastes, in order to increase your profits. Research shows that 70% of all data collected within a drug manufacturing plant is not used (Manzano and Lange, 2018). Pharma 4.0 intends, through the implementation of new digital technologies (Exposed previously as Key Technologies involved in Industry 4.0), to eliminate this data waste. By digitizing and generating connected processes that offer data in real and constant time, decision-making processes will be faster, and personalized treatments would be possible.

The transformation of the current pharmaceutical manufacturing processes into ones based on this approach is a complex process. Requires, besides technological implementation changes within their culture and organizational structure. It is essential to first fully understand the current process implemented. Then understand the Pharma 4.0 operating model and finally start the transformation guide by an established strategy.

The Pharma 4.0 Operation model described by ISPE offers a classification of 4 different areas that must be interconnected in the company to achieve the development of this model. Including, resources, information systems, culture and organisation and process. ISPE creates this operating model in order to provide a guide to pharmaceutical companies in the incorporation of Pharma 4.0 principles. This model is based on Industry 4.0 Maturity Index (described in previous section), generated by the German Academy of Science and Engineering (ACATHEC). The Maturity Index is a systematic guide to lead companies in their adaptation processes to Industry 4.0. This Model is explained in more detail in section 1.6 Maturity Index.

A brief description is presented below:

1. Resources: this area refers to all physical resources within the company. How used the personnel, facilities, tools, machinery, digital technologies. In addition, they must have the characteristic of being able to connect physical resources to digital resources.
2. Information systems: These are all the technological communication systems to achieve interconnected processes.

3. Organization and processes: The organizational structure of the company must be based to achieve the correct flow of all the elements that must be developed within Pharma 4.0.
4. Culture: Pharma 4.0 is a path that must be planned and implemented by the entire company, it is not only a managerial job or of certain business areas. It is a joint effort that demands that the culture of the company be focused on it.

The main difference between Industry 4.0 and Pharma 4.0 is the specificity of their scope. While Industry 4.0 intends to digitalize any manufacturing processes, Pharma 4.0 is focused on the drugs manufacturing process. Integrating the main characteristic that differentiates this industry from others, compliance with strong regulatory systems. Due to the nature of this industry, compliance with quality processes is essential. ISPE describes the concept of Pharma 4.0 as the union between the Industry 4.0 capabilities with ICH Q10. Which is a model designed to ensure GMP compliance in a product lifecycle in order to create an effective quality management system.

Currently key factors within manufacturing processes such as control process parameters (CPPs), control quality attributes and validation protocols are developed by human personnel who are in charge of data acquisition and with the help of statistical programs transform these data into useful information for decision making. However, these parameters can be affected by internal and external factors and even by their very nature. Hence, the true understanding of the quality of your manufacturing processes should not only consider these values as the absolute truth without considering the factors that may affect them. All the aspects that intervene within a manufacturing environment must be considered as a whole to generate fast, flexible and agile production processes.

1.8 Pharma 4.0 in Ireland

The pharmaceutical industry in Ireland has evolved very quickly. Currently there is a mix of large global companies, suppliers, and small corporations. Which have a robust value chain in their production processes. Based on the evolution that it has reflected; it can be said that it will continue to grow to a great extent. As stated previously, Ireland offers a strategic geographic location, skilled workforce presence and very attractive tax rates from a business perspective. Therefore,

Ireland can be considered as the ideal setting for the development and implementation of Pharma 4.0.

However, in the literature search process, regarding current level of acquisition of Pharma 4.0 in pharmaceutical companies in Ireland, no significant literature can be or study can be found. On an overview of the level of technological presence in the manufacturing industry in general and under the industry 4.0 approach can be generated. In this way, when analyzing Ireland's Industry 4.0 Strategy 2020-2025: It is reflected that the strategy is aimed at the fact that the manufacturing companies in the country intend to adopt the concept of industry 4.0 as one of their competitive advantages. To maintain a productive and sustainable industry. However, this strategy is focused on the preparation of the company prior to the digital evolution, that is, to the adoption of Industry 4.0. The projection indicates that by the year 2025 the manufacturing companies in Ireland will have the necessary capabilities to scale up the path of technological transformation. Furthermore, it is a strategy for the future, so we can conclude that in general the manufacturing industry in Ireland is still at a level of preparation towards these new technological models. As a result, and based on what has been described, we can predict that Pharma 4.0 is not expected to be at high levels of development within companies.

Pharma 4.0 implementation is not an easy path, requires time and planning. The strategy is a start but there are still many more steps to follow to achieve this transition successful. The following chapter will present the results obtained in the development of an investigation to identify the level of presence of Pharma 4.0 currently in the pharmaceutical industry of Ireland

CHAPTER 2

2. RESEARCH METHODOLOGY

The main purpose of this study was to identify the current the technological Readiness of Pharmaceutical Companies in Ireland facing Pharma 4.0. For the purpose of this study, readiness level was measured by quantifying the current presence of this Pharma 4.0 operating model in Irish pharmaceutical companies. This was accomplished through the use of a technological capabilities measurement system, which scores different established indicators to measure the presence of Pharma 4.0. Additionally, triggers and challenges to adhere to the operation model were identified.

This chapter describes the methodological approach used, design, method of data collection, sampling technic, and methods of analysis. In addition, conceptual framework regarding Industry 4.0 maturity index models and detailed explanation of the technological capabilities measurement system implemented.

2.1 Methodological approach.

Quantitative research methodology was followed in this study. Since, allowed to find valid numerical representation for stablished variables (Borgstede and Scholz, 2021). This approach also recognized specific variables contained in a certain study frame, correlate variables and control the sampling method and the environment in which the data is collected (USC, 2021). Primary research was implemented in order to study specify indicators, which were measured to determine the level of Pharma 4.0 readiness. In addition, by using this approach, due to its quantitative nature, replicate it a different sample will be possible.

A qualitative approach would not have provided the possibility to numerically calculate the level of readiness. In addition, interviews will not have provided the possibility of accessing a large number of participants in a short period of time. Hence, quantitative research with a survey as a data collector method was a Good fit for this study. Provided specific data needed for statistical analysis in a short period of time, comparison of variables and apply a technological capabilities measurement system as a tool evaluation were executed**.**

2.2 Design and Method of Data Collection

The data collection process was carried out through surveys. Currently, in Ireland are approximately 85 manufacture pharmaceutical companies (IDA, 2021). The number of participants that was intended to access through the surveys was 50. For the purpose of this study, the focus will be directed towards the production processes, although Pharma 4.0 integrates other functional areas such as logistics, marketing, and management, they will not be analysed, in the present study.

Convenience sampling technique adopted, selecting employees from the manufacturing area of pharmaceutical companies. It was Accessed to different company positions such as quality managers, validation engineers, production managers, process operators, engineers, and other personnel who are involved in the production area. Professional network LinkedIn and e-mail was used to send the survey. The voluntary filing was required and it was specified that all the information collected would be exclusively used for the purpose of this research and finally, the questionnaire was submitted for ethical approval prior to its implementation.

2.3 Technological capabilities measurement system.

In order to satisfy the objective of the study, a technological capabilities measurement system was applied. This capability measurement tool was made based on the selection and measurement of indicators presented in The Acatech Industry 4.0 Maturity Index and IMPULS - Industry 4.0 Readiness. Which are instruments that describe a series of capabilities that must be acquired by companies in order to successfully adopt this approach. They are presented in overlap levels, where the first level represents the lowest maturity, that is, a poor development of capabilities, and the highest level represents the most mature company, with a robust presence of capabilities.

The Industry 4.0 Maturity models are guides for companies to ensure successful integration of digital processes in order to evolve to the Industry 4.0 model. I this way, considering Pharma 4.0 is based on Industry 4.0 principles these Maturity models can be applied.

Industry 4.0 Maturity models evaluate companies using different approaches to identify strengths and weaknesses that will be used for the benefit of adopting digital capabilities. There are different Maturity models available for companies, each one with its own area of focus, maturity stages, evaluation criteria, etc. For the purpose of illustration, 4 of these models are presented with a brief description are presented in Table 2.

No.	Maturity Model	Description
1.	Acatech Industry 4.0 Maturity Index	Presents six stages of maturity and assesses capabilities in 4 structural areas. It aims to provide a guide for each company to develop its strategy. Focused on manufacturing companies.
2.	IMPULS—Industry 4.0 Readiness	Presents six maturity levels and assesses capabilities in 6 different dimensions. Aimed to explore abilities in mechanical areas.
3.	Digital Readiness Assessment Maturity Model (DREAMY)	Presents five maturity levels and it is focuses on manufactory industry.
4.	The Connected Enterprise Model	Presents five maturity levels with no dimensions stablished.

Table 2. Maturity models description.

Source: (Dikhanbayeva et al., 2020)

In general, according to the literature review conducted, Maturity models tend to provide scales of 6-4 different levels of maturity with similar characteristic but with differences in the evaluation approaches. For the development of this study, The Acatech Industry 4.0 Maturity Index and IMPULS - Industry 4.0 Readiness, for the creation of the technological capability measurement tool used in the present study. These were selected due to strong similarity of maturity levels and evaluation criteria that both offer. Subsequently, collected data is used to locate the Irish pharmaceutical industry in one of the six different digital maturity stages offered by Acatech Maturity Index and scored Criteria % proportioned in IMPULS - Industry 4.0 Readiness.

As explained in 1.6 Maturity Index section, Acatech Industry 4.0 Maturity Index exposed six different stages that represent different levels of digital maturity (Computerisation, Connectivity, Visibility, Transparency, Predictive capacity, Adaptability). Each stage depends on the previous

one and describe the digital capabilities that must be fulfilled in order to obtain it. Capabilities are grouped in four different structural areas; resources, information systems, culture, and organizational structure. The same structural areas and capabilities are evaluated at each stage, however, as the stage progresses the amplitude of the capabilities increases.

Acatech Industry 4.0 Maturity Index was used in order to identify 19 different indicators. Distributed in 4 different structural areas: Resources, information systems, culture, and structure organization. Table 3 describes in detail the structural area under evaluation, the capabilities evaluated and the indicator used to carry out a quantitative evaluation.

(STRUCTURAL AREA)	CAPABILITIES	INDICATOR
Resources	Digital Capability	❖ Number of Pharma 4.0 Technologies in use. ❖ Level of existing employee's digital competencies. ❖ Availability of data acquisition through sensors.
	Structure communication	❖ Existence of collaborative software or groupware
Information Systems	Information processing	❖ Existence of automated data analysis in real time. ❖ Existence of cyber-physical systems (CPS). ❖ IT department organization.
	Integration	❖ Level of information systems' integration
Organizational Structure	Organic Internal Organization	❖ Level of flexibility in assigning tasks and work areas. ❖ Level of collective decision making. ❖ Existence of motivational goal systems ❖ Level of employee integration in making decision processes
	Dynamic collaboration in value networks	❖ Level of focus on satisfying customers
Culture	Wiliness to change	❖ Existence of a strategy for the evolution to pharma 4.0 ❖ Level of culture of learning from errors. ❖ Level of openness to change. ❖ Level of Continuous professional training.
	Social Collaboration	❖ Level of democratic management presence. ❖ Level of open communication

Table 3. Structural Areas, Capabilities and Indicators.

Source: (Schuh et al., 2020), (IMPULS, 2021)

The survey's purpose was to evaluate digital capabilities are present in the companies that participated in the study. It was made up of 15 closed-ended drop down and ranking questions grouped according to the following criteria:

1. Section 1: This section aims to verify that the participant is part of Pharma workforce and the general knowledge and presence of pharma 4.0 in the participant's organisation.
2. Section 2: Resource's category is evaluated, assessing the current presence of Pharma 4.0 technologies and the existence of collaborative software for effective communication.
3. Section 4: Information systems category is evaluated, acquiring information on data acquisition technology, presence of cyber-physical systems (CPS), structure of the IT department and current level of integration of information systems.
4. Section 5: Organisational structure category is evaluated, obtaining information on the degree of flexibility in assigning tasks, presence of motivational systems and the level of integration of the employee in decision-making processes.
5. Section 6: Culture category is evaluated; participants were asking to rank the level of openness to change and open communication in their companies.

2.4 Sampling Technique

Two of the most widely used methods of sampling are probability sampling and non-probability sampling. Both trigger a number of sampling techniques that are implemented according to the objectives and nature of the research (Etikan *et al.*, 2015).Convenience sampling technique was used, which is part of the Non-probability sampling methodology.

Convenience sampling technique, is generally used for studies that analyse quantitative data and that the target participants meet specific practical criteria such as easy accessibility for the researcher, geographic proximity or open participation by the participants (Shantikumar, 2010). Furthermore, convenience sampling is recognised as accepted method study topics that are relatively new, such as Pharma 4.0 (Gurung, 2017).

Participants capable of generating valuable data for this study are participants who form part of the workforce of drug manufacturing companies in Ireland specific within production processes. Therefore, the present study obtained data through primary research using a survey and the target respondents represented a big simple size. Convenience sample technic allowed to reduce the sample size base on the accessibility and wiliness to take part without losing the necessary profile to obtain valuable data.

Convenience sampling faces a disadvantage, bias can occur, therefore the results obtained may not be really representative. However, this risk can be eliminated by means of a significantly representative sample selection system, that is, an effective distribution of the questionnaire (Skowronek and Duerr, 2009). Therefore, the survey was sent strictly to participants who met the specified target through the development of a professional network using LinkedIn, primary research implementation. Access to 39 participants from representing different pharmaceutical companies was accomplished.

A professional network through LinkedIn was constructed prior survey implementation, which allowed access to participants efficiently and quickly. First, a number of 70 companies that fit the desired profile in the study was identified. Subsequently, a participant's search was carried out assuring that they work for the identified companies and fulfil the sample criteria. Finally, a first connection point was established, explaining the purpose of the study and inviting to participate in it. Surveys were sent to participants who agreed to complete the survey. This approach allowed an effective distribution of the survey and avoided having duplicate company representations.

2.5 Method of Data Analysis

Convenience sampling data are used in this research, hence descriptive statistics becomes the most convenient approach for the analysis of these data (Price, 2013). Descriptive statistics is used in the present study.

The first question of the questionnaire was designed with the purpose of verifying that the participants met the established sample criteria, therefore only data that met the criteria was used. The rest of the 14 questions in the survey were quantitative in nature, and a numeric value was

assigned to each answer in order to calculate the maximum score value of each structural area described in Table 4.

Table 4 presents the weighted and maximum possible score value for each structural area, this value was obtained by assigning a numerical value to each answer and adding the scores belonging to the questions made based on the indicators for each structural area.

Max score for each structural area		
Structural Areas	**Score (%)**	**Max Total score**
Resources	21%	32
Information systems	21%	53
Organizational structure	26%	25
Culture	32%	34

Table 4 Maximum score for each structural area.

Source: Calculated by author.

The numerical values of each question were determined as follows:

1. Affirmative and negative questions, numerical value 1 was assigned for affirmative responses.
2. Questions where it was requested to indicate a certain level, a gradual numerical value from 0 to the maximum number depending on the options in response were assigned. The number 0 was assigned to the response with the poorest representation.

3. Responses to questions with Likert scale format, a number value was assigned to each agreement point, and the total score for each question was calculated by adding the score of each statement.

To identified the overall technological readiness a numerical criteria score was stablish. Levels were also assigned for a better visualization of the 6 maturity stages and to represent the similarity of the two maturity models used. Refer to Table 5.

Stage	Readiness level	Criteria %	Criteria score
Computerisation	Level 0	0	0
Connectivity	Level 1: Beginner	0<X<30	0< Points<38
Visibility	Level 2: Intermediate	30<X<65	38< Points<82
Transparency	Level 4: Experienced	65<X<80	82< Points<101
Predictive capacity	Level 5: Expert	80<X<90	101< Points<113
Adaptability	Level 6: Top performer	90<100	113< Points<126

Table 5 Technological Readiness Stages and criteria

Source: (Schuh et al., 2020) (IMPULS, 2021).

Pharma 4.0 and Industry 4.0 are concepts that are still in their implementation process within the manufacturing industries, for this reason, there are so many instruments that provide digital maturity measurement. Since there is no generic and effective formula to be able to measure or implement these trends (Sony and Naik, 2019). These models can be acquired according to the nature of the strategy and objectives of the company. On the other hand, there are authors who, through the analysis of technological maturity models, offer key ingredients to evaluate the preparation for Industry 4.0 for organizations (Sony and Naik, 2019), or describe a model aimed at the current preparation to acquire a future readiness versus Industry 4.0 (Botha, 2018). However, although this literature is a valuable contribution, it is not within the scope of this study that seeks to measure the current level of preparation that pharmaceutical companies have to adopt the Pharma 4.0 model.

CHAPTER 3

3. FINDINGS

A total of 80 surveys were sent through the LinkedIn professional network, in order to meet the target sample of 50 participants. Finally, 39 responses to the survey were obtained, all representing a different Irish Pharmaceutical company.

Follow the same question grouping criteria used in survey, the primary research results are presented below

3.1 General knowledge and presence of pharma 4.0.

The first section of the survey was aimed to discover the level of knowledge about the Pharma4.0 concept.

Five different levels of knowledge were established as a measurement factor in the survey:

1. Zero.
2. Novice.
3. Basic.
4. Intermediate.
5. Advanced knowledge.

Figure 3 Illustrates the results obtained. The level of knowledge about the Pharma 4.0 concept was represented mainly as Novice (30.8%), Basic (25.6%) and Intermediate (28.2%).

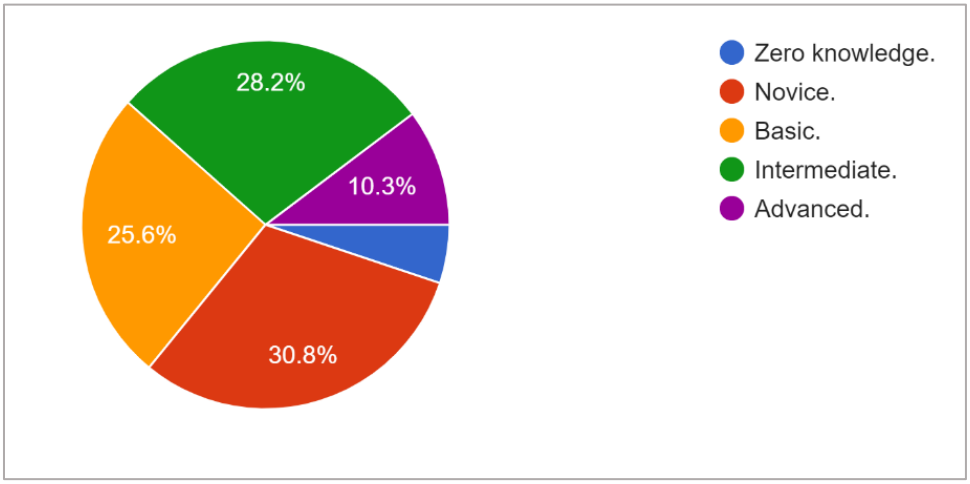

Figure 3. Knowledge about Pharma 4.0 concept

Based on the mean of the data, in general, the level of knowledge about Pharma 4.0 is Basic. In this context, the average knowledge about Pharma 4.0 concept is Positive. Most of the respondents (95%) affirmed that they are familiar with the concept. Within this group, only the rest 5% of the total number of the participants indicated zero knowledge regarding the concept. However, results stated that this knowledge has on average a basic level of mastery.

3.2 Resource's structural area indicators.

The structural area of Resources was evaluated by measuring the following indicators:

3.2.1 Number of Pharma 4.0 Technologies in use:

A list of 9 Pharma 4.0 technologies was presented, participants were asked to indicate which ones are in use within the production processes of their companies.

Figure 4 indicates that all these referred technologies, generally are present within the production processes of the participant's company.

The majority of respondents stated a big presence of automated process, with a representation of 74.4% compared with the other technologies.

Data acquisition through sensors, PAT tools, Real-time Data exchange, could Data Storage have a representation of between 30-34%. Finally, the technologies with less presence are artificial intelligence, Internet of things both with 15.4%, and Big Data with 10.3%. Additionally, 82% of the participants indicated a limited range of 1 to 3 Pharma 4.0 technologies present in their company.

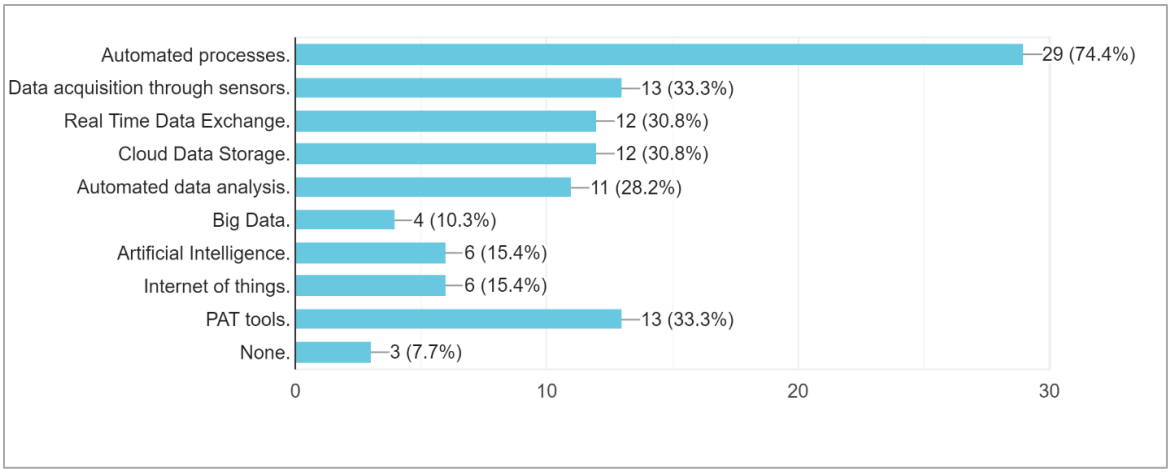

Figure 4. Pharma 4.0 Technologies in use

Therefore, there is a focus on the automation of the process through the implementation of innovative machinery, which facilitates repetitive tasks in the processes. However, the presence of technologies that offer human-machine connection is reflected in less than a third compared to automation.

3.2.2 Level of existing employee's digital competencies.

Figure 5 illustrates the level of satisfaction expressed by the participants, regarding the digital competencies that employees possess. Seven digital competencies were evaluated; IT Systems, IT Security, Data collection, Data Analysis, Decision-Making based on data, Communication systems and Process understanding.

Outstanding that an average 88% of the participants indicated that employees certainly possess these competencies. However, 43% of the same group stated that the domain of the competencies is inadequate.

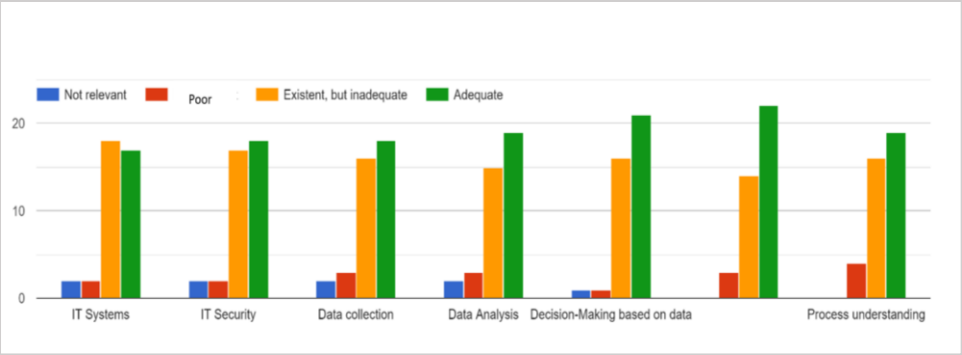

Figure 5. Digital Competences in employees

It seems, that employees' knowledge of technological competencies is in general vastly basic. This indicates that companies are not focused on strengthening these competencies and, on the other hand, there is no proactivity on the part of employees in updating themselves with technological competencies.

3.2.3 Availability of data acquisition through sensors.

Figure 6 shows that 77% of the participants affirmed the presence of data acquisition through sensors within their companies' production processes. However, it is stated that the production process is not fully covered with this technology. On the other hand, a small representation (12.8%) indicated that the entire production process has the capacity of acquiring data through sensors.

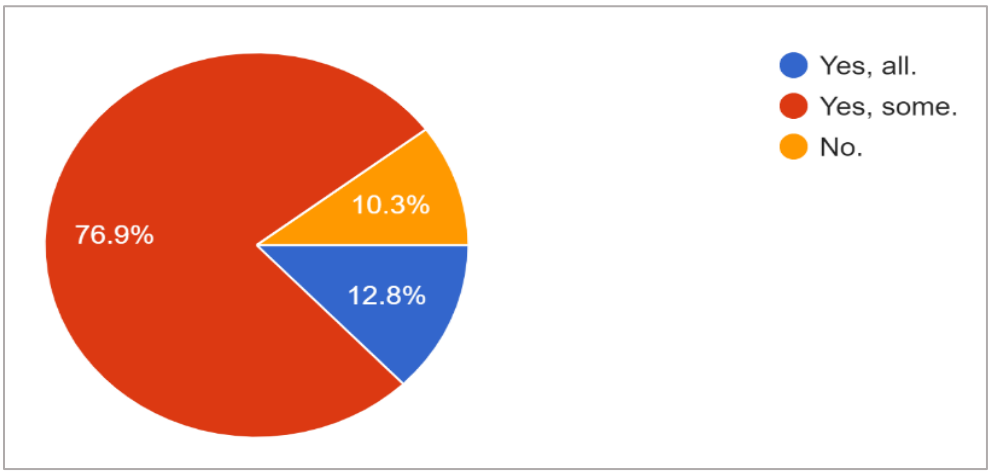

Figure 6. Data Acquisition Through Sensors.

Data collection is a fundamental factor within Pharma 4.0. The companies participating in this study indicate that they actually possess data collection systems through sensors. This means that the data is measured and sent to computer systems that will later convert the data into information. However, these systems are isolated, that is, only in certain areas. As a result, there is no data collection from start to finish in your production processes through this system.

3.2.4Existence of collaborative software or groupware.

Figure 7 indicates the evaluation made by the participants on the presence of collaborative software within their companies. As can be seen 15.4% of the participants affirmed that such software completely exists and works as a communication system for the entire company. Against 61.5% who indicated that these software are only used in certain areas.

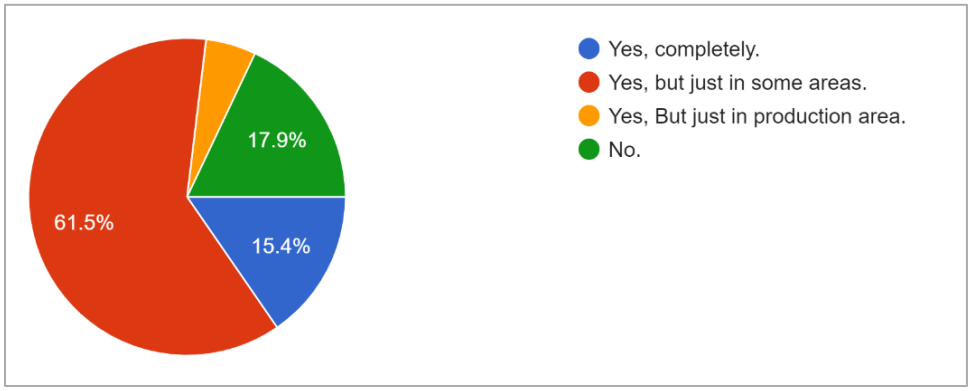

Figure 7. Existence of collaborative Software

The main reason for implementing Collaborative software or groupware as part of the strategy towards the adoption of Pharma 4.0 is the generation of efficient communication between employees. Which, thanks to this software, will be documented, will avoid redundancy and will eliminate data waiting times. Based on the results, we could conclude that if these systems exist in the participating companies. However, communication is limited to each area of the company.

3.3 Information systems' structure area indicators.

The Information system structure area was evaluated by measuring the following indicators:

3.3.1Existence of automated data analysis in real time.

The results show that 33.3% have autonomous production systems that respond based on data obtained in real time. In turn, with the same representation percentage of 33.33%, they affirm the presence, but in a trial period for future implementation. Compared to 20.5% who have a total connection not only in production processes. No existence in any company area was express by 12.8% of the participants. See Figure 8.

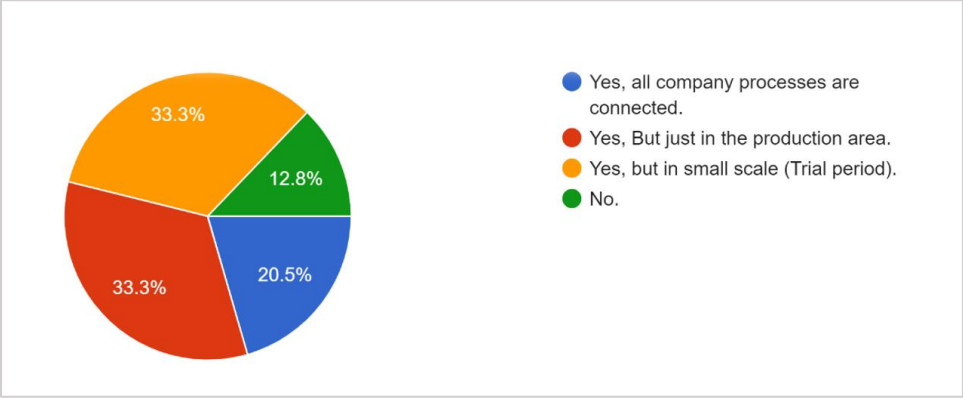

Figure 8. Real time data acquisition.

3.3.2 Existence of cyber-physical systems (CPS).

CPS were measured according to the presence of three specific functionalities in the production machinery; Machinery manipulation through IT systems, remote communication and interconnection between all the machinery. Approximately 55% affirm that the presence of the three functionalities exists up to some extent but not completely, compared to 38% indicated total

availability. The rest indicate no presence of CPS. See *Figure 9.*

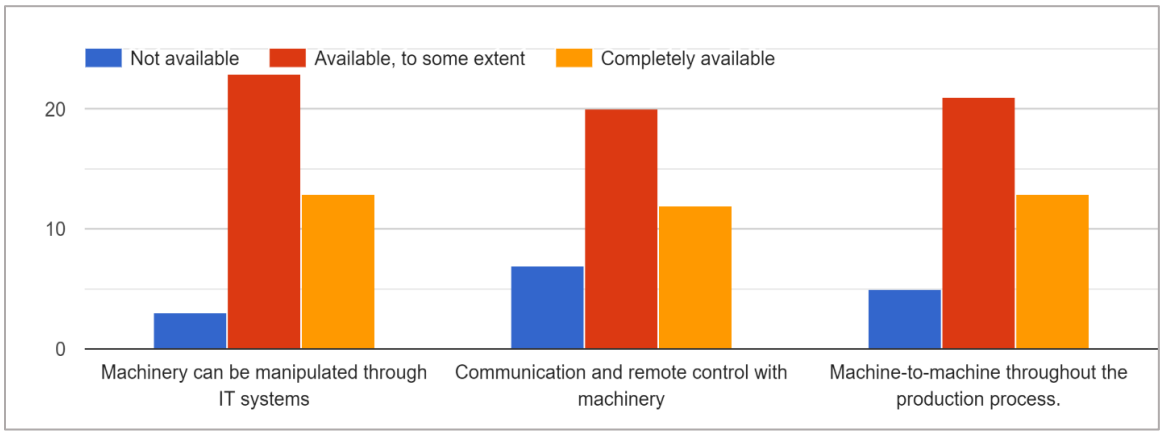

Figure 9. Existence of CPS

3.3.3 IT department organisation.

Figure 10 displays the organization of the IT department. Reflecting that 64% of companies have only one IT department that covers the entire company. A quarter of the participants indicated that this service is provided by an external provider. Only a minimum representation of 7% has specific IT departments assigned to each different company area.

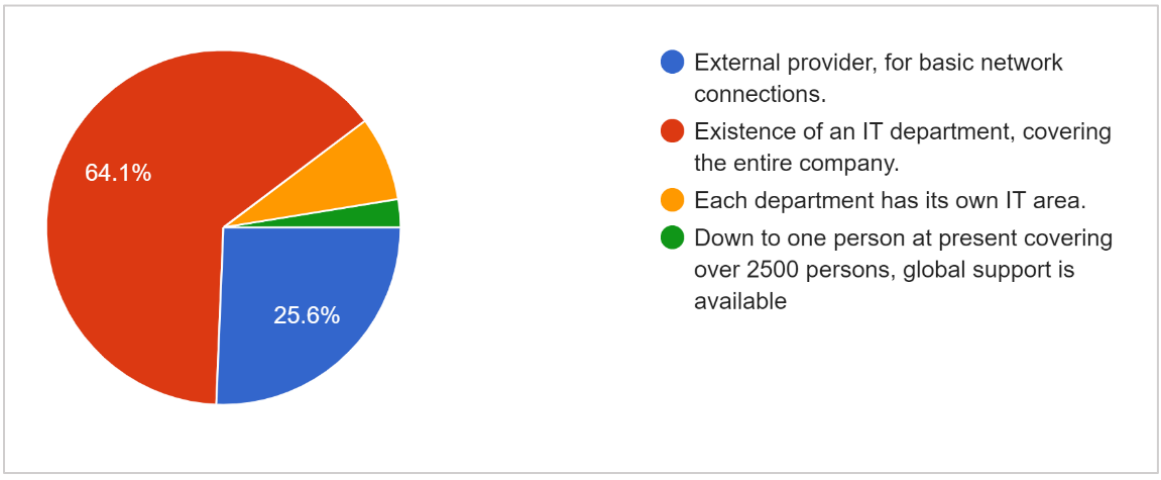

Figure 10. IT department organisation.

3.3.4 Level of information systems' integration

Information systems ensure access to all available data and immediate use, throughout the drug manufacturing process. Participants were asked to indicate the level of integration of these systems within the value chain of their companies. The following seven digital capabilities were measured using an agreement Likert scale:

- The information is available in online storage systems. (Cloud)
- Technologies capable of analysing large amounts of data.
- Ability to predict future scenarios through data analysis.
- Total data control throughout the process, providing the ability to adapt the process at all times.
- Production and the entire value chain are connected.
- The data collected is transformed into information that turns into process improvement.
- Strong presence of IT security.

The results indicate that the capability with the greatest presence is the ability to transform the data into process improvement, reflecting 70% of the participants agree or Somewhat Agree with the statement. Followed by strong presence of IT security with a representation of 62% of responses under the same agreement category rank.

Ability to predict future scenarios through data analysis (15%) and ability to adapt the process at all times (12%), were the capabilities with the least positive affirmation. Results are detail in *Figure 11*.

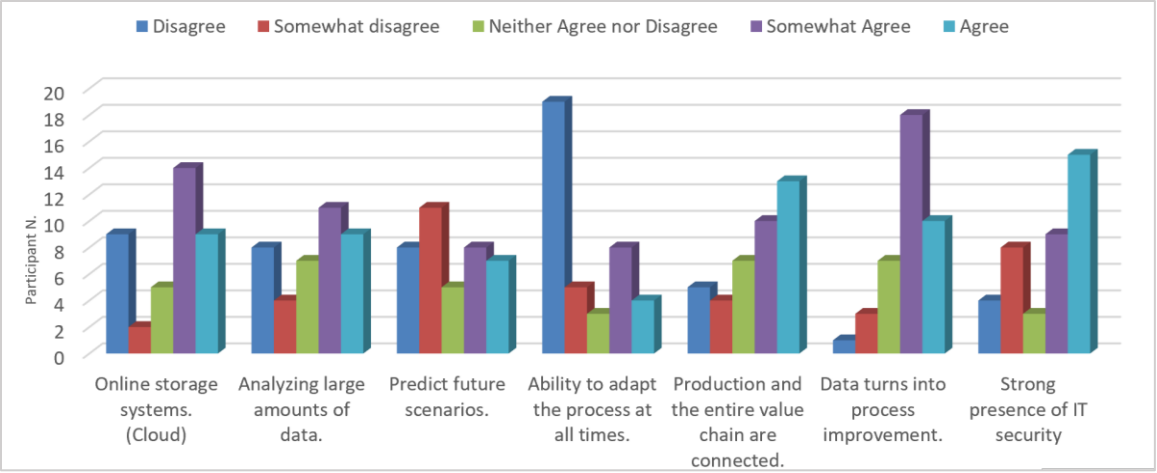

Figure 11. Information Systems' Integration

In general, the participants indicated that the integration of information systems is poor within the production processes of their companies. The two categories with the greatest presence are the use of data for process improvements and IT security.

3.4Organizational structure's structural area indicators.

The indicators in this category were evaluated using an agreement Likert scale. As Figure 12 shows, the responses, in general, agreed with the variables raised. The majority of answers provided were in the Somewhat agree- Agree range. Noticing, 34 of the participants agree to a certain extent that the company's approach is aimed at customer benefit, 24 of these agreed entirely. Seduced by 32 of the participants, expressed motivational systems are implemented in their companies. And finally, it is observed that collective processes for decision-making is a characteristic of the structural organization of the participating companies, with a total of 28 participants that indicate the presence of this indicator.

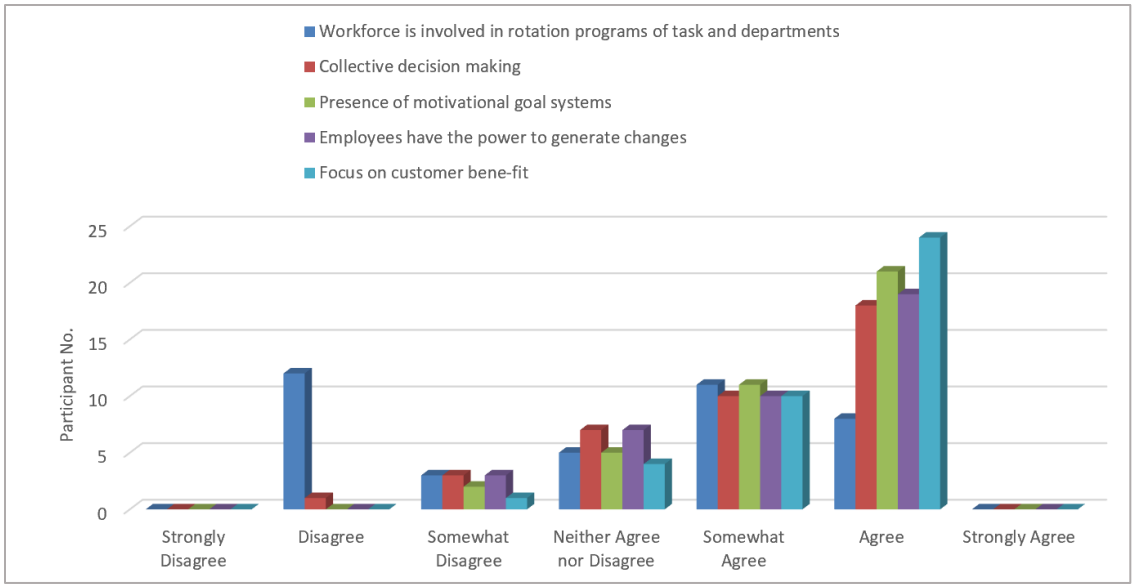

Figure 12. Organisational structure.

3.5 Culture' structural area indicators.

The culture structure area was evaluated by measuring the following indicators:

3.5.1 Existence of a strategy for the evolution to pharma 4.0.

Participants were asked directly if a strategy in favour of Pharma 4.0 was implemented, currently in development, in a pilot phase or if it does not exist. According to the results, strategies in development and no strategy had the same representation percentage (30.8%). Therefore, only 7.7% indicated that the strategy has already been implemented. See Figure 13.

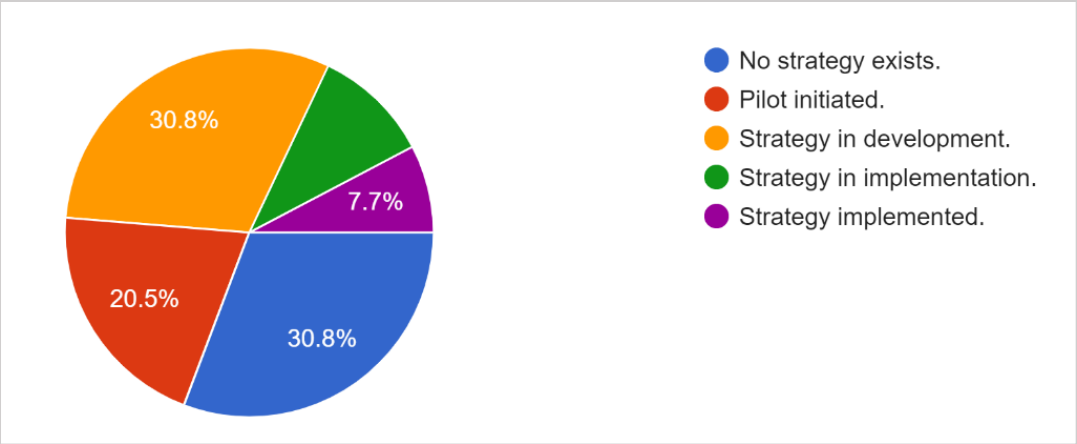

Figure 13. Existence of a Pharma 4.0 implementation strategy

The successful implementation of a strategy for Pharma 4.0 adoption is a crucial. However, as reflected in the data obtained, such strategy is not present in the companies or they are in pilot phases.

The last 5 indicators were evaluated together, asking the participants to evaluate the level of agreement or disagreement on 5 different statements regarding the culture of their company. See Figure 14.

The majority of the responses were favorable to the statements raised. The participants declared that within their company's culture, mistakes are discussed and learned from them (59%), it is indeed a culture open to innovative changes (67%) and finally, continuous training of staff is perfomed(61%). They also affirmed the presence of a Democratic management style (45%) and Knowledge-sharing is a fundamental principle in the entire workforce (46%).

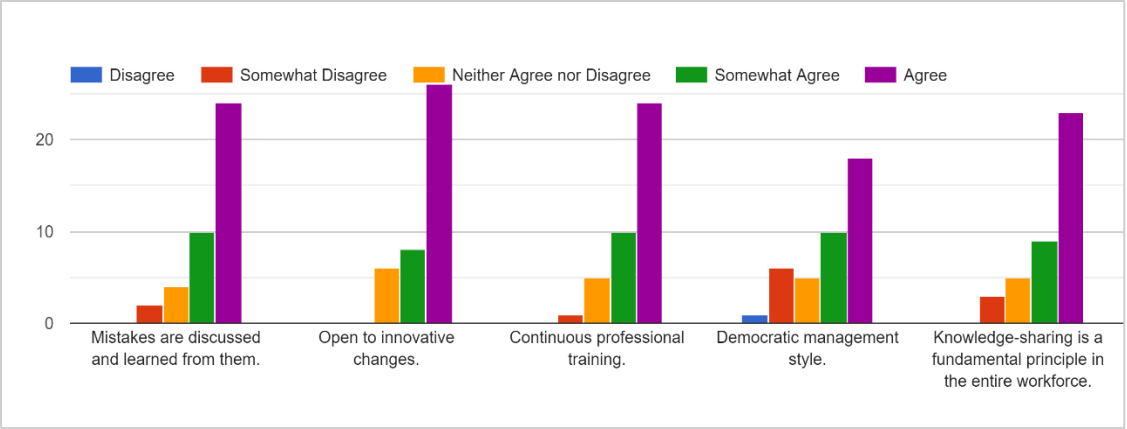

Figure 14. Company's culture

In general, there is a very positive attitude on the part of the participants towards the current culture of their company. All the characteristics evaluated on the company's culture were indicated as present by the participants.

3.6 Pharma 4.0 overall readiness level

Table 6 presents the average results of the four structural areas. The results of each one was added and the total compared with the score criteria presented in *Table 4*. The analysis reveals that based on the average of the data provided, the companies participating in this study are at a Level 2 or intermediate, that is, in the visibility stage.

Structural Areas	Max Total score	Survey scores
Resources	35	22
Information systems	53	18
Organizational structure	25	16
Culture	34	24
TOTAL		80

Table 6. Overall score.

Figure 15 Shows a more detailed breakdown of Pharma 4.0 overall readiness level. The data revealed that all the companies participating in this study are located in Level 2 (74%) or level 3 (26%).

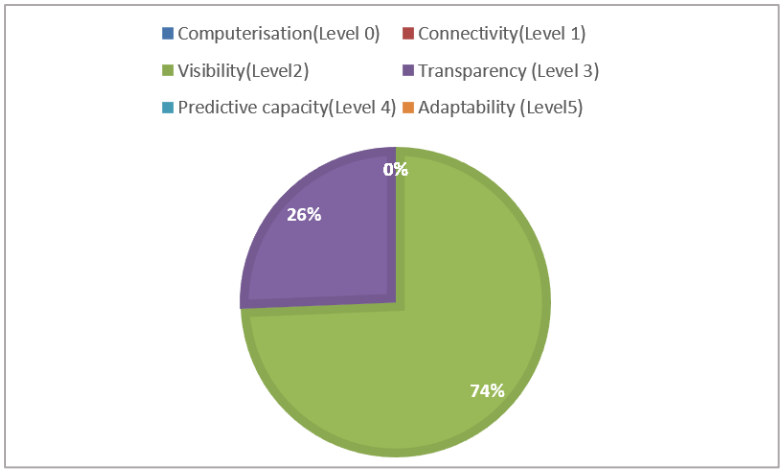

Figure 15. Overall Readiness level score.

Main triggers and challenges faced for the evolution to pharma 4.0

In order to identify the main triggers, eight different possibilities were provided. The participants were asked using a likelihood Likert scale to rate them. See Figure 16. Triggers for the evolution to Pharma 4.0

The main identified triggers are Increase in productivity (59%), greater efficiency in decision-making processes (30.8%), followed by innovation in goods and services and can be used as a competitive advantage (25.6%). Make Regulatory compliance easy, new business opportunities and rapid adaptation capacity were stated with a final representation of (10.3%).

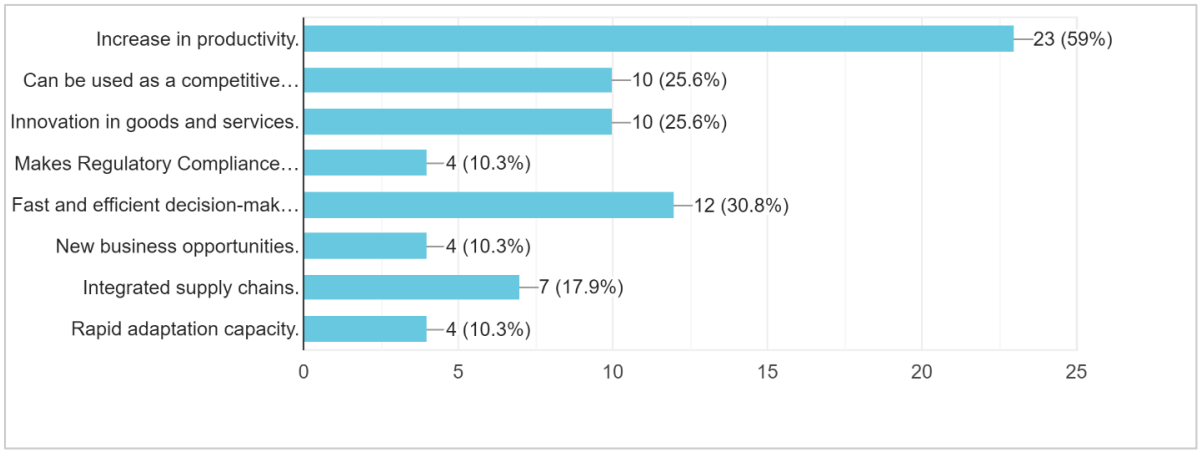

Figure 16. Triggers for the evolution to Pharma 4.0

Conversely, participants were asked to rate seven different challenging possibilities in the adaptation of pharma 4.0. Using a likelihood Likert scale.

Responses predominantly indicated costs involved for implementation (65.6%), implications in adopting new technologies (37.5%), regulatory concerns (34.4%), insurance of resistance to change (28.1). See Figure 17.

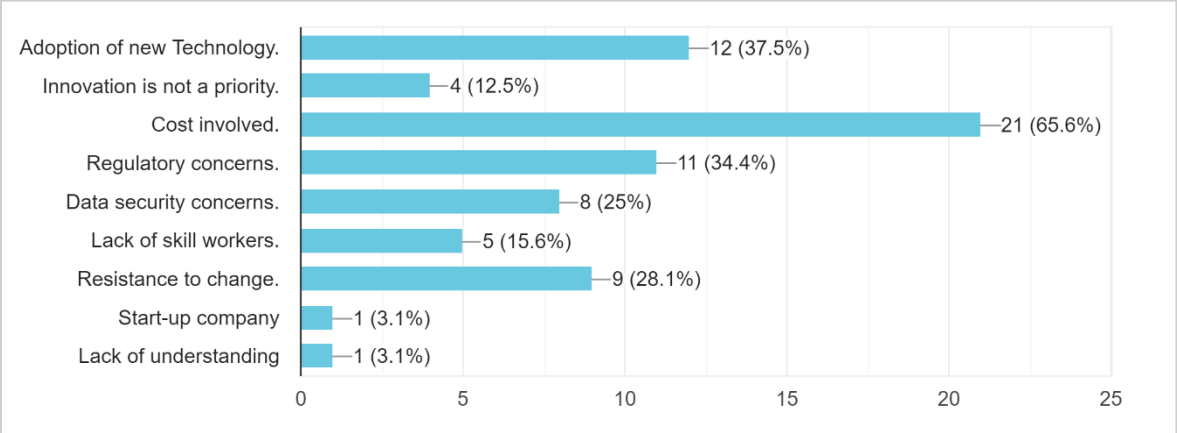

Figure 17. Challenges faced for the evolution to pharma 4.0

CHAPTER 4

4.ANALYSIS

Overall, the data obtained from companies that participate in the study reveal to have a basic Knowledge of Pharma 4.0 concept. In other words, there is familiarization with the concept but not to a wide extent. In this way, Irish pharmaceutical companies are aware of the existence of the model and the benefits it offers. Increase in productivity was stated as the main motivator for this companies to evolve to this model. However, it is believed that the costs required for a successful implementation represent the biggest challenge, as a result this factor delays the development of the model.

As indicated in Table 5, the structural area of resources presents 63% accomplishment regarding its overall readiness level. This percentage indicates to what extent the evaluated indicators were accomplished by the participant companies. For the purpose of this study, the technological presence and IT workforce skills were evaluated. Based on data obtained the only technology with a significant presence was automated systems. This is not surprising, since the automation of repetitive tasks within the manufacturing process is a trend that has been in implementation during the last years. Since companies began to use technologies to increase their productivity and reduce human intervention. However, automation only represents the foundations to continue advancing forward digitalization. From a Pharma 4.0 perspective, technological resources must have the capacity to generate human-machine and machine-machine connexion. As well the ability to generate and process data in real-time. Based on the results, this state is poorly represented. There is no considerable representation of technologies that generates the connexion between the existence automated systems and humans. Showing a representation of less than a third compared to automation. Connexion machine-machine was representing in 38% of the participants 'companies. No relationship was identified between the two variables. This means that in general the production processes certainly have a representation of both types of connections but in isolation. Regarding data collection, the results yielded a positive but limited representation. Since having automated processes these technologies can include sensors that record the critical parameters of the process. But they don't cover completely the process, it indicates that they are a system for collecting isolated data.

The lower representation was granted to the information systems, a structural area with 33% accomplishment in regarding its overall readiness level. Hence, the information obtained from process data is minimally used to support the decision-making process.

Evaluated data shows that participants (70%) affirmed that the currently obtained data in their companies is transform into process improvements. As mentioned above, the participants indicated the precedent of automated systems capable of acquiring data through sensors. Therefore, companies are using data that they currently have the ability to generate and transform into improvements. So far this is a positive statement, however, when evaluating the rest of the indicators it is found that. CPS is present but not in all manufacturing stages, therefore they are isolated. And, the trend is that one IT department covers the whole company. Therefore, the data obtained is transformed into information that supports decision-making in specific areas or phases of the processes. There is no end-to-end data connection, therefore the information analysis is sectioned. This is due to the fact that there is no CPS coverage in the whole process and that the IT departments are not robust.

The implementation of the Pharm 4.0 model, it requires a correct organisational structure that establishes rules aimed at achieving this approach. Based on the findings, 64% accomplishment regarding its overall readiness in companies' organisation structure was reflected. For instance, it can be stated that on average companies' organization structure presents an organic nature. This is that employees are motivated through the development of motivational systems, they are involved in making decisions and can generate changes. Therefore, companies' employees do not face substantial limitations that affect their performance and there is also an awareness of the degree of individual responsibility and the power they have to make internal changes.

Culture is the structural area with the largest representation (71%) regarding its overall readiness level. Culture is a crucial part to evolve to Pharma 4.0 model. Is not possible to become an agile company without direct employees to this same objective. One of the main tools for the entire company to work in accordance with the adaptation of Pharma 4.0 is the establishment of a solid strategy that describes and evaluates the activities to be developed to achieve this evolution. According to the data obtained, an average of half of the participants indicated that the strategy is in development or in its pilot stage versus 30% which does not exist at any level. This is an encouraging result as it indicates that companies are aware of the importance of a strategic implementation prior to the evolution to Pharma 4.0

Subsequently, the rest of the indicators were evaluated very positively, affirming that the culture of your company elements such as the openness to innovation, learning from mistakes, continuous

training is in greater presence. In general, we can indicate that the perception of the employees about their companies is very positive. Workforce presents strong foundations to pursue a clearly established strategy on the way to Pharma 4.0, which becomes an advantage for the pharmaceutical industry in Ireland its

Finally, the study has Shown that, all companies participating in this study are located in Level 2/ Visibility stage or level 3 /Transparency stage. The majority of the companies in the visibility stage belongs to the companies that stated not having a Pharma 4.0 strategy or that is in development.

CHAPTER 5

5 CONCLUSIONS AND RECOMMENDATIONS

The speed at which innovative technologies are being developed is increasing. In fact, the period between each industrial revolution is getting shorter. This means that new technologies are developing faster and therefore are required much more than before. Shaping the way, the manufacturing industry operates. As a result, the industry is in constant change generated by the interaction of different variables, such as fluctuations in the global economy, the increase of competitors and of the demand for innovative products. Resulting, in companies search of strategies that allow them to remain profitable. Thus, technological acquisitions allow them to develop competitive advantages over their competitors and at the same time generate more productive and agile processes. Processes that allow them to adapt to the constant change in this fluctuating industry.

Industry 4.0 is an operating model that offers to transform the way in which industrial companies operate, providing the ability to have adaptable, efficient, and secure processes through the integration of technologies, communication systems, and data processing. Therefore, becomes the ideal company's path to survive in the fluctuating environment in which we are submerged.

The pharmaceutical industry is strictly monitored by regulatory bodies. For instance, is not an easy task to stablish strategies that allow them to be companies adaptable to change. As consequence, Pharma 4.0 operation model had emerged. This model provides the principles stablished in Industry 4.0 to Pharma sector. The pharmaceutical industry is a very complex part of the industry which requires a millionaire investment and long periods of time for the launch of a single product. Adding the external variables that shape this industry such as the demand of faster processes, lower costs, and more personalized treatments. Without compromising the quality and safety of the final product. Apparently, the adaptation of this operating model is not an easy path for Irish pharmaceutical companies today.

The pharmaceutical industry in Ireland is a very powerful industry, with a large representation as exporter in the European continent. However, despite this robust image, this industry is still in the early stages of implementing Pharma 4.0 as an operating model.

The adaptation of current manufacturing processes that are focused on technologies that emerged in a previous industrial revolution into the new Industry 4.0 revolution is the new challenge for pharmaceutical companies. Years have passed and the presence of this new approach is not yet reflected in an encouraging level.

According to the present research, the main challenge for the Irish pharmaceutical industry, is related to costs and logistics involved in the acquisition of new technological systems. However, it is considered that one of the most difficult challenges in the evolving path to Pharma 4.0 is the change of employee mindset. In this way, employees should be first creating value to the company. Companies should start to focus on strengthen employee IT skills, employees must have a good understanding of the processes that are developed throughout the company, in order to have an entire vision and to be able to identify improvement processes in a more productive way.

Therefore, a successful implementation of the Pharma 4.0 model does not only depend on focusing on technology investment. It is not possible to implement the model without involving the workforce, and make them feel comfortable and understand the new approach. Therefore, and based on the results of this study, Ireland has a very favourable position. Since indicators measured that the labour force was the area that was expressed with the greatest satisfaction. Indicating that the workforce has important characteristics for the development and implementation of Pharma 4.0. The culture of participant companies has an open approach to innovation, learning from mistakes, sharing information. However, although the results have a positive trend, the result is linked to a basic level of readiness.

Despite, the representation of the pharmaceutical industry in this study is only represented by a sample and does not cover the entire industry. The results revealed that there is a significant presence of automated processes that involve machine-machine connections. In charge of developing processes that were previously carried out by humans. Which is a favourable technological first step in direction to digital transformation. However, challenges are faced in their data acquisition and processing. Indicating, existence of collection data process but is it not being used to support the decision-making processes or generate predictions.

Overall, the study showed that the Irish pharmaceutical industry is at the visibility stage which represents the basic level of Pharma 4.0 implementation. This indicates that pharmaceutical companies in Ireland have a presence of technology capable of creating visible processes. Through data collection and processing. However, this visibility is focused on obtaining data for analysis of specific stages of the process. Which are requested by regulatory bodies, or analysis to generate a specific improvement in the process.

Below, recommendations are provided to the companies participating in this study, which are focused on achieving a successful evolution to the Pharma 4.0 operating model.

- Although in general a familiarity with the term Pharma 4.0 exists, the scope is very narrow. Knowledge about the model and its benefits should be extended to all employees of the company. As well as the expectations that the model has about the workforce.

- Performed a study to identify the current digital maturity level of the company. Each company has its own characteristics defined by its objectives, vision, and culture. Therefore, strengths and weaknesses can be identified and quantified through the use of industry-generic Industry 4.0 Maturity Index. In this research, the Acatech Industry 4.0 Maturity Index and IMPULS Industry 4.0 Readiness were used. However, more tools like these are available with different methodologies. According to the suitability of the company, it must be selected.

- Generate a strategy for the creation of an agile workforce. To achieve this goal, it is necessary to constantly train employees in the use and importance of digital systems, create job rotation programs and deliver power to generate change. In this way, employees will increase innovation, their work efficiency, and constant change will be part of the work culture.

- Generate a strategy towards Pharma 4.0. Prior planning is essential when starting the evolution. In this way you can set goals and measure the degree of compliance.

- Increase investment in the implementation of digital systems. It is necessary for the integration of digital systems that allow them to increase the visualization of their processes. As the results indicate, the processes are being carried out in isolation. Through the implementation of digital software such as PLM, ERP, and MES, the processes will be understood and integrated.

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APPENDIXE

Survey Questions

1. **Are you employed by a manufacturer pharmaceutical company in Ireland?**
    - Yes
    - No
2. **What do you consider the level of knowledge of the pharma 4.0 concept in your company?**
    - Zero knowledge
    - Novice
    - Basic
    - Intermediate
    - Advanced
3. **Is there any strategy in place for the implementation of Pharma 4.0 within your company?**
    - No strategy exists.
    - Pilot initiated.
    - Strategy in development.
    - Strategy in implementation.
    - Strategy implemented.
4. **Has your company implemented any of these Pharma 4.0 digital capabilities within their processes? (multiple options can be selected)**
    - Automated processes.

- Data acquisition through sensors.
- Real Time Data Exchange.
- Cloud Data Storage.
- Automated data analysis.
- Big Data.
- Artificial Intelligence.
- Internet of things.
- PAT tools.
- None.

If your previous answer were None or if 1-3 capabilities were selected, please continue with question 5, if not go to question 6.

5. **What might be the main reason for the delay in adopting the Pharma 4.0 digital capabilities described previously?**

	Very Likely	**Likely**	**Unlikely**	**Very Unlikely**
Adoption of new Technology				
Innovation is not a priority				
Cost involved				
Regulatory concerns				
Data security concerns				
Lack of skill workers				
Resistance to change				

Other, please describe: _____

6. **What do you consider might be the main reason for adopting the Pharma 4.0 digital capabilities?**

	Very Likely	Likely	Unlikely	Very Unlikely
Increase in productivity				
Can be used as a competitive advantage				
Innovation in goods and services				
Makes Regulatory Compliance Easier				
Fast and efficient decision-making processes				
New business opportunities				
Integrated supply chains				
Rapid adaptation capacity				

Other, please describe: _____

7. **How do you assess the level of knowledge of the following digital competencies in employees?**

	Poor	Good	Existent, but inadequate	Adequate
IT Systems				
IT Security				
Data collection				
Data Analysis				
Decision-Making based on data				
Communication systems				
Process understanding				

8. **Are the data generated during the production processes collected automatically through technological systems (Sensor technology)?**

    - Yes, all.
    - Yes, some.
    - No.

Groupware refers to the set of informatics systems that facilitates the communication between groups of employees for the structural organization of their activities**.**

9. **Does your company implement groupware as a communication system?**

    - Yes, completely
    - Yes, just in some areas.
    - Yes, just in the production area.
    - No.

One of the main characteristics of processes based on Pharma 4.0 is the ability to constantly acquire and analyse data (in real-time) to support automatic decision-making processes, without human intervention.

10. **Does your company implement an autonomous production process that responds based on real time data acquisition?**

    - Yes, all company processes are connected.
    - Yes, just in the production area.
    - Yes, on a small scale (Trial period).
    - No.

11. **How would you assess the production machinery according to the following functionalities?**

	Not available	Available, to some extent	Completely available
Machinery can be manipulated through IT systems			
Communication and remote control with machinery			
Machine-to-machine throughout the production process.			

12. How is the IT department organized within your company?

- External provider, for basic network connections.
- Existence of an IT department covering the entire company.
- Each department has its own IT area.
- Other: _____

Pharma 4.0 also involves the integration of information systems. In this way, different areas of the company are connected and the data collected is processed and transformed into information that will be used to make improvements throughout the manufacturing process.

13. When thinking about your company's integration information systems, how strongly do you agree or disagree with the statements?

	Strongly Disagree	Disagree	Somewhat disagree	Neither Agree nor Disagree	Some what Agree	Agree	Strongly Agree
The information is available in online storage systems. (Cloud)							

Technologies capable of analyzing large amounts of data.							
Ability to predict future scenarios through data analysis.							
Total data control throughout the process, providing the ability to adapt the process at all times.							
Production and the entire value chain are connected.							
The data collected is transformed into information that turns into process improvement.							
Strong presence of IT security							

14. Referring to your company organizational structure, how strongly do you agree or disagree with the statements?

	Strongly Disagree	Disagree	Somewhat disagree	Neither Agree nor Disagree	Somewhat Agree	Agree	Strongly Agree
Workforce is involved in rotation programs of task and departments							
Collective decision making							
Presence of motivational goal systems							
Employees have the power to generate changes							
Focus on customer benefit							

15. **When thinking about your company culture, how strongly do you agree or disagree with the statements**

	Strongly Disagree	Disagree	Somewhat disagree	Neither Agree nor Disagree	Some what Agree	Agree	Strongly Agree
Mistakes are discussed and learned from them.							
Open to innovative changes.							
Continuous professional training.							
Democratic management style.							
Knowledge-sharing is a fundamental principle in the entire workforce.							

Other, please describe: _____